S U M M A R Y

Studies in phenols and biphenols . - Phenols are the starting materials for the synthesis of many natural products and products of commercial importance and hence are substances of great synthetical importance. They have been extensively studied and subjected to a number of reactions. Substituted phenols especially those with negative substituents and biphenols have been studied to a lesser extent. The present work deals with the chloromethylation of various resorcinol derivatives and biphenols, synthesis of biflavonyls from biphenols, succinoylation and phthaloylation of biphenols and preparation of Mannich bases from 4,4'-dihydroxy biphenyl.

The thesis begins with a brief introduction on phenols and biphenols and then goes on to the description of the present work.

Chapter II deals with the chloromethylation of some phenolic compounds. Chloromethylation is an excellent tool in the synthetic work as the chloromethyl group undergoes reactions with various reagents, for example, the chlorine of the chloromethyl group can be replaced by hydroxy, cyano, methoxy and acetoxy groups. On Sommelet reaction the chloromethyl group can be replaced by the formyl group and, on oxidation it can be readily converted into an acid and on reduction to a methyl derivative.

The present work deals with the chloromethylation of negatively substituted resorcinols and of 2,2'-and 4,4'-biphenols.

Resacetophenone on chloromethylation with one or more moles of paraformaldehyde gave a mixture of products from which no pure compound could be isolated. Its dimethyl ether with 1.2 moles of paraformaldehyde in dioxan at room temperature, however, afforded the 5-chloromethyl derivative which on oxidation with alkaline potassium permanganate furnished 4,6-dimethoxy isophthalic acid as seen by direct comparison with the product obtained on oxidation of methyl 2,4-dimethoxy-5-acetyl-benzoate with alkaline permanganate. On chloromethylation with excess of paraformaldehyde in glacial acetic acid at room temperature the 3,5-dichloromethyl derivative was obtained.

Methyl β-resorcylate on chloromethylation with one mole of paraformaldehyde did not afford a pure product but with an excess of paraformaldehyde in dioxan at room temperature it furnished the 3,5-dichloromethyl derivative. The dimethyl ether of methyl β-resorcylate with 1.2 moles as well as with an excess of paraformaldehyde at 80-90° provided the 5-chloromethyl derivative which on oxidation gave the known 4,6-dimethoxyisophthalic acid.

Chloromethylation of 4-nitro resorcinol did not provide a pure product, but its dimethyl ether furnished with one mole and with an excess of paraformaldehyde, the 5-chloromethyl derivative which on oxidation afforded 2,4-dimethoxy-5-nitrobenzoic acid, identical with an authentic specimen prepared by methylation of the known 2,4-dihydroxy-5-nitrobenzoic acid. The chloromethyl

derivative on reduction with tin and hydrochloric acid yielded 2,4-dimethoxy-5-methylaniline identical with the product obtained on nitration of 2,4-dimethoxy toluene and subsequent reduction with tin and hydrochloric acid. Alongwith the chloromethyl derivative a chlorine free product was also isolated. Its analysis indicated that it might be methylene bis-(2,4-dimethoxynitrobenzene).

2-Nitroresorcinol on chloromethylation with one mole of paraformaldehyde gave 3-chloromethyl-2,6-dihydroxynitrobenzene. With an excess of paraformaldehyde at room temperature it afforded 3,5-dichloromethyl derivative. The dimethyl ether of 2-nitroresorcinol on chloromethylation at 70-80^{0} furnished 2,6-dimethoxy-3-chloromethylnitrobenzene.

4,4'-Dihydroxy biphenyl on chloromethylation using 2.5 moles of paraformaldehyde in dioxan afforded the 3,3'-di(chloromethyl) derivative. 4,4'-Dimethoxy biphenyl on chloromethylation with two or more moles of paraformaldehyde in 90 % acetic acid on a steam bath also afforded the 3,3'-dichloromethyl derivative which on oxidation gave an acid identical with the one obtained on oxidation of 3,3'-diacetyl-4,4'-dimethoxy biphenyl with alkaline permanganate.

2,2'-Dihydroxy biphenyl did not provide a pure product on chloromethylation. Its dimethyl ether however, gave the 5,5'-dichloromethyl derivative at room temperature. On oxidation it afforded an acid identical with 2,2'-dimethoxy biphenyl-5,5'-dicarboxylic acid prepared by the Ullmann

reaction on methyl 3-iodo-4-methoxy benzoate and subsequent hydrolysis of the ester.

The chloromethyl derivatives were subjected to the Sommlet reaction with hexamethylene tetramine. The methyl ethers provided formyl derivatives whereas the hydroxy compounds gave unworkable products.

Most of the chloromethyl derivatives have been converted into their acetoxymethyl derivatives and some have also been converted into cyanomethyl and methoxy methyl derivatives.

In Chapter III the synthesis of some biflavonyls starting with biphenyl derivatives has been described. 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, Iso-ginkgetin, Sciadopitysin, Kayaflavone and Sotetsuflavone are some of the important biflavonyl derivatives isolated from plants.

Several biflavonyls have been synthesised so far through a simple or Crossed Ullmann reaction on the appropriate iodoflavones. The yields in the final stage are very low. It was thought of interest to see if the biflavonyls could be synthesised by starting with a suitable biphenyl derivative and building up the flavonyl rings simultaneously on both the phenyl rings. The present

work deals with the synthesis of some 3,3'''- and 6,6''-biflavonyls by this approach.

4,4'-Dimethoxy-3,3'-diformyl biphenyl on condensation with 2-hydroxy acetophenone in the presence of alcoholic potassium hydroxide gave 2,2'''-dihydroxy-6,6''-dimethoxy-3,3''-bichalconyl which on refluxing with selenium dioxide in amyl alcohol gave 6,6'''-dimethoxy-3,3'''-biflavonyl. This was also obtained by an alternate synthesis as follows.

2-Hydroxy acetophenone was condensed with 2-methoxy-5-iodo benzaldehyde in the presence of alcoholic potassium hydroxide, and 2'-hydroxy-2-methoxy-5-iodo chalcone obtained. This on refluxing with selenium dioxide in amyl alcohol gave 2'-methoxy-5'-iodoflavone which on Ullmann reaction gave a product identical with the one described above.

Similarly 2,2'''-dihydroxy-4,4''',6,6''-tetramethoxy-3,3''-bichalconyl was prepared by the condensation of 4,4'-dimethoxy-3,3'-diformyl biphenyl with 2-hydroxy-4-methoxy acetophenone. This gave 6,6''',7,7''-tetramethoxy-3,3'''-biflavonyl when refluxed with selenium dioxide in amyl alcohol. The same product was obtained by condensing 2-hydroxy-4-methoxy acetophenone with 2-methoxy-5-iodo-benzaldehyde and converting the resulting 2-hydroxy-2,4'-dimethoxy-5-iodochalcone into 2,7-dimethoxy-5-iodoflavone by heating with selenium dioxide as before. The iodoflavone on Ullmann reaction gave the biflavonyl described above.

2,2'-Dimethoxy-5,5'-diformyl biphenyl gave 2,2'''-dihydroxy-4,4''-dimethoxy-3,3''-bichalconyl on condensation with 2-hydroxy acetophenone. This gave 4,4'''-dimethoxy-3,3'''-biflavonyl on cyclisation as above. This was also obtained by the Ullmann reaction on 4'-methoxy-3'-iodoflavone obtained from 2'-hydroxy-4-methoxy-3-iodochalcone which in turn was obtained by the condensation of 2-hydroxy acetophenone with 4-methoxy-3-iodo benzaldehyde.

2,2'''-Dihydroxy-4,4,4'',4'''-tetramethoxy-3,3''-bichalconyl obtained from 2,2'-dimethoxy-5,5'-diformyl biphenyl and 4-methoxy-2-hydroxy acetophenone gave 4,4''',7,7''-tetramethoxy-3,3'''-biflavonyl as usual. The same biflavonyl was also obtained when 2'-hydroxy-4,4'-dimethoxy-3-iodochalcone obtained from 2-hydroxy-4-methoxy acetophenone and 3-iodo-4-methoxy benzaldehyde, was converted into 4,7-dimethoxy-3'-iodoflavone and the latter then subjected to Ullmann reaction.

6,6'''-Dihydroxy-3,3'''-bichalconyl was prepared from 4,4'-dihydroxy-3,3'-diacetyl biphenyl by condensing with benzaldehyde and then converted into 6,6''-biflavonyl as before. The same biflavonyl was also obtained when 4,4'-dihydroxy-3,3'-diacetyl biphenyl was subjected to Kostanecki-Robinson benzoylation at 210-15° and the 3,3'''-dibenzoyl derivative of the biflavonyl obtained was hydrolysed with 2 %alcoholic sodium hydroxide. 6,6''-Biflavanonyl was also prepared from the above bichalconyl by refluxing with alcoholic hydrochloric acid.

4,4''',-Dimethoxy-6,6''-biflavonyl was prepared from 6,6''',-dihydroxy-4,4''-dimethoxy-3,3''',-bichalconyl which was obtained by the condensation of 4,4'-dihydroxy-3,3'-diacetyl biphenyl with anisaldehyde.

Chapter III deals with the Friedel-Crafts succinoylation and phthaloylation of biphenyl derivatives. Succinoylation of 4,4' and 2,2'-dimethoxy biphenyls has been carried out by Baddar et al. with one mole of succinic anhydride and they isolated the B-2-methoxy-5-(p-methoxyphenyl)benzoyl- and B-4-methoxy-3-(o-methoxyphenyl)benzoyl propionic acids respectively. They have not reported the succinoylation of the above dimethoxy biphenyls with excess of succinic anhydride. It was thought of interest to see whether the succinoylation takes place in both the rings simultaneously and to cyclize the diketonic acids if obtained to the corresponding bitetralonyls.

4,4'-Dimethoxy biphenyl on Friedel-Crafts succinoylation with excess of succinic anhydride gave the 4,4'-dimethoxy biphenyl-3,3'-bis-(γ-keto butyric acid). The structure of the above product was proved by converting it into the known 4,4'-dimethoxy biphenyl 3,3'-dicarboxylic acid. The above bis-γ-keto butyric acid derivative after Clemmensen reduction and cyclization with polyphosphoric acid gave 5,5'-dimethoxy-8,8'-bitetralonyl.

Under similar condition 2,2'-dimethoxy biphenyl gave 2,2'-dimethoxy biphenyl-5,5'-bis-(γ-keto butyric acid) since it gave the known 2,2'-dimethoxy biphenyl 5,5'-dicarboxylic acid on oxidation. The bis-γ-keto butyric acid

on reduction and cyclization gave 7,7'-dimethoxy-8,8'-bitetralonyl, the structure of which was established by converting it into 2,2'-dimethoxy-1,1'-binaphthyl by Huang-Minlon reduction and aromatization with selenium dioxide.

In the course of this work it is found that the ketonic acid m.p. 229-30° reported by Badder et al. is not the B-(4-methoxy-3-o-methoxyphenyl benzoyl) propionic acid, but the 2,2'-dimethoxybiphenyl-5,5'-bis-γ-keto butyric acid.

With one mole of succinic anhydride 2,2'-dimethoxy-biphenyl gave 4-methoxy-3-(2-methoxy phenyl)benzoyl propionic acid which on further succinoylation gave the 2,2'-dimethoxy biphenyl-5,5'-bis-γ-keto butyric acid described above.

2,2'-Dimethoxy biphenyl on Friedel Crafts phthaloylation gave 2,2'-dimethoxy-5,5'-bis-(o-carboxy-benzoyl)biphenyl which on Clemmensen reduction gave 2,2'-dimethoxy-5,5'-bis-(o-carboxybenzyl)biphenyl which on treatment with 95 % sulphuric acid gave 2,2'-dimethoxy-1,1'-bianthronyl. The structure of the above bianthronyl derivative was established by converting it into the known 2,2'-dimethoxy-1,1'-bianthraquinonyl.

In Chapter IV Mannich reaction on some phenolic compounds has been described. Mannich reaction has proved to be an important tool in synthetic organic chemistry. Some of the Mannich reaction products can be converted into a variety of compounds such as acetoxy methyl, methoxy-

methyl,hydroxy methyl etc. and some of the Mannich bases ~~or their reduction products~~ are found to be important medicinal agents.

Not much work on the application of the Mannich reaction to biphenol derivatives appears to have been reported. Therefore it was thought of interest to study the application of Mannich reaction to 2,2' and 4,4' biphenols with various primary and secondary amines.

4,4'Dihydroxy biphenyl when subjected to Mannich reaction with benzyl amine and paraformaldehyde gave the bioxazinyl derivative which on refluxing with alcoholic hydrochloric acid gave 4,4'-dihydroxy-3,3'-dibenzyl aminomethyl biphenyl. Similarly aniline gave the oxazino derivative which on refluxing with alcoholic hydrochloric acid gave 4,4'-dihydroxy-3,3'-dianilinomethyl biphenyl. Morpholine,piperidine and dimethylamine on condensation with 4,4'-dihydroxy biphenyl and paraformaldehyde gave 4,4'-dihydroxy-3,3'-dimorpholinomethyl biphenyl,4,4'-dihydroxy-3,3'-dipiperidinomethyl biphenyl and 4,4'-dihydroxy-3,3'-di-(dimethylaminomethyl)biphenyl respectively. All the amino methyl derivatives described above gave the same 4,4'-diacetoxy-3,3'-diacetoxymethyl biphenyl.

4,4'Dihydroxy biphenyl when subjected to Mannich reaction with one mole each of morpholine, piperidine and dimethylamine gave 4,4'-dihydroxy-3-morpholinomethyl-4,4'-dihydroxy-3-piperidinomethyl biphenyl and 4,4'-dihydroxy-3-dimethylaminomethyl biphenyl respectively. The above mono substituted derivatives on

further Mannich reaction gave the di-substituted derivatives already mentioned above.

Appendex Synthesis of 3,3'-dimethyl-5,5'-bibenzofuranyl

4,4'-Dihydroxy-3,3'-diacetyl biphenyl was condensed with bromoacetic ester and the resulting di-ester derivative was hydrolysed and cyclised to get the 3,3'-dimethyl-5,5'-bibenzofuranyl.