CHAPTER I

GENERAL INTRODUCTION

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Biphenyls are the starting materials for the synthesis of many compounds of therapeutic value and also commercialy important compounds. Although small amounts are present in coal tar the biphenyl of commerce is obtained by the pyrolysis of benzene. One successful scheme has been to pass benzene vapour through molten lead at temperatures of about 750 ^{0}C.

Therapeutic and commercial uses :

Druckrey[1] found that 4,4′-dihydroxybiphenyl has estφrogenic as well as antimiotic activity. Kraft[2] reported that 2-hydroxy-,3-hydroxy-,4-hydroxy-,2-hydroxy-4-nitro-, 4,4′-dihydroxy-,4,4′-dihydroxy-3,3′-dichloro- and 4,4′-dihydroxy-3,3′,5,5′-tetrachloro-biphenyl are bactereostatically active. Biphenyl derivatives are effective on mycobacterial metabolism[3]. Soap in bar and liquid form is rendered germicidal by incorporating 0.5 to 10 % of a halogen derivative of 2,2′-dihydroxybiphenyl such as 5,5′-dichloro,5,5′-dibromo or 3,3′,5,5′-tetrabromo[4]. Johnson and Mussell[5] reported that 3,3′-dipropyl-, 3,3′-diallyl- and 3,3′-bis(2-methallyl) 4,4′-dihydroxybiphenyl are effective in combating coccidiosis. Halogenated 2,2′-dihydroxybiphenyls are found to possess a good protective action against termites. Massarani et al.[6] reported that 3(4-biphenyl)acrylic acid has got anti-inflammatory activity. Derivatives of biphenylφ such as

2,2′-dihydroxy-3,3′-5,5′-tetrachloro-,4,4′-dihydroxy-3,3′-5,5′-tetrachloro-, 2-nitro-,4′-nitro-,4-chloro- and 2,4-diamino- were found to have fungistatic activity[7,8]. 2,2′-Dihydroxybiphenyl derivatives, especially the 3,3′,5,5′-tetrachloro derivative, are found to be effective as moth proofing agents for wool[9].

2,2′-Dihydroxybiphenyl is used as an antioxidant in the oxidation of lubricating oil[10] as well as in the catalytic oxidation of rubber solutions[11]. Hydroxybiphenyls are also used in synergistic antioxidant combinations which effectively inhibit thermal oxidation of polyolefins[12]. Biphenyls can be used in the preservation of citrus fruits during storage and shipment[13].

4,4′-Dihydroxybiphenyl and its 3,3′-dimethyl derivative are found to be useful as stabilizers for polyesters[14] and for vinylchloride polymers[15]. Substituted dihydroxy biphenyls having the general formulae $\left[3,4,5\text{-R (OH) R}'C_6H_2\right]_2$ where R and R′ are alkyl groups are effective stablizers for cracked gasolines[16].

Octachlorobiphenyl[17] is used in the preparation of self-extinguishing fire resistant epoxy resins and octabromobiphenyl[18] is found to be effective in making polyethylene fire-proof. Isojima et al.[19] reported that derivatives of biphenyl such as 3,3′-dihydroxy-,4,4′-diamino-, N,N′-diethyl-3,3′-dimethoxy-4,4′-diamino- and N,N′-dibutyl-3,3′-dimethoxy-4,4′-diamino- are effective in making polypropylene fibres resistant to heat and light.

Voskresenskii et al.[20] found that biphenyl has got both plasticizing effect as well as compatibility.

The most important of the biphenyl derivatives is benzidine, an intermediate in the manufacture of various azodyes. The effectiveness of ultraviolet absorbers in improving the fastness to light of level-dyeing dyes, such as Celliton disperse and Genacryl basic types, on Dacron, is found to be distinctly increased when biphenyl is used as a carrier[21].

Conant and Seifert[22] found that Dowtherm A, a eutectic mixture of biphenyl and biphenyl oxide can be used as liquid or vapour upto 750°F with no corrosion in mild steel, no decomposition and no toxicity. Chlorinated biphenyl is used to prepare a resin by which the concrete surface is treated to prevent the evaporation of water during hardening[23].

General methods for the synthesis of biphenyl derivatives :

(1) Ullmann synthesis[24] : A general method for the preparation of a biphenyl derivative is the Ullmann reaction. It consists in the condensation of two molecules of an aromatic halide in the presence of a metallic agent with the elimination of a metal halide.

$$RX + R'X + M \longrightarrow RR' + MX_2$$

This synthesis is of general applicability and has found wide use in the preparation of many symmetrical

and unsymmetrical biaryls and polyaryls which would otherwise be difficult to obtain. The success of the Ullmann reaction is dependent upon the nature of the aromatic halide. The order of reactivity of halogens is I > Br > Cl. The work done on the Ullmann reaction upto 1945 has been reviewed by Fanta[25].

Certain electronegative groups in the ortho or para positions with respect to the halogen atom activate the latter through - T effect[26]. The nitro group is the most effective activator. An ortho or para carboxyl or carbalkoxyl group also activates markedly. Substituents which exert a + T effect would be expected to lead to deactivation when they occupy positions ortho or para to the halogen atom.

A decrease in yield probably because of the side reactions is generally observed when certain groups are present in the aromatic nucleus. eg.-NH_2 ; -$NHCOCH_3$, -$NHCH_3$, -SO_2NH_2, -$SO_2NHC_6H_5$, -COOH and -OH which can give rise to amination, decarboxylation or ether formation as a side reaction. Bulky substituents in positions adjacent to the reactive halogen hinder biaryl formation.

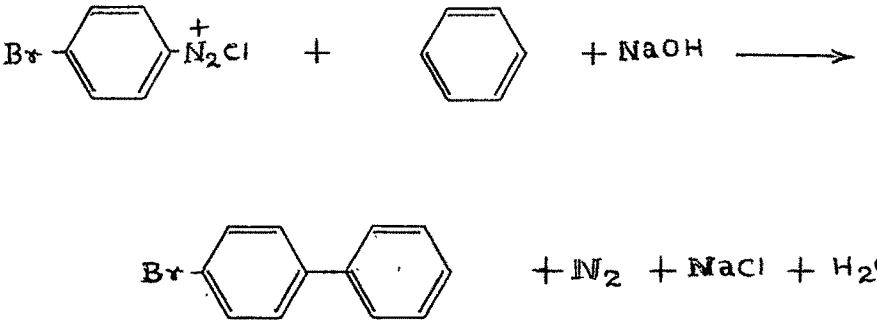
Unsymmetric biaryls[27] have been successfully synthesised by a cross Ullmann reaction with appropriate halogen derivatives. When a mixture of two aromatic halides RX and R′X are subjected to Ullmann reaction R-R and R′-R′ are also formed along with the desired R-R′

and hence the success of the cross Ullmann reaction depends upon the selection of proper starting materials and optimum ratio of the two starting materials.

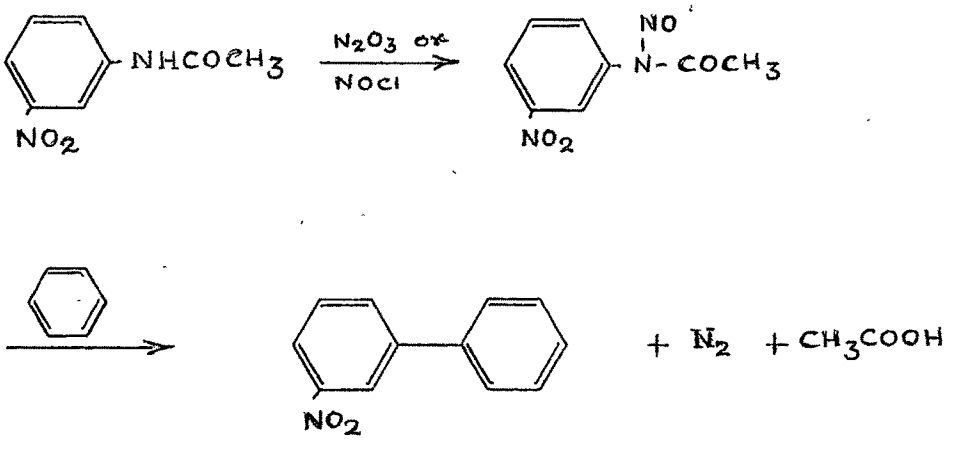
(2) Biphenyls can be prepared by the catalytic hydrogenation of halogenated aromatic compounds. Bromobenzene with 5 % potassium hydroxide in methyl alcohol in the presence of palladium-calcium carbonate at 140° gave about 10 % of biphenyl in 6 hrs. When other substituents are present in benzene nucleus, the yield of biaryl is governed by the ease of elimination of the halogen. o-Dibromobenzene remains unchanged or on more energetic treatment yields benzene, while p-dibromobenzene gave terphenyl with biphenyl and a halogenated quarterphenyl. p-Diiodobenzene behaved in the same way[28].

(3) Bamberger[29] and Kuhling[30] have developed a method for the preparation of biaryls by replacing the amino group of an aromatic amine by an aryl group. The amino group of aromatic amines can be replaced by two general procedures : (a) by the reaction of the aryl diazo hydroxide or acetate with aromatic compounds and (b) by the reaction of nitrosoacetylamine with aromatic compounds.

In the first method an aromatic amine is diazotised to get the diazonium salt which is then reacted with an aromatic compound in the presence of sodium hydroxide[31].



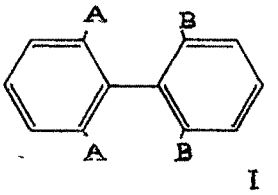
In the second method the aromatic amine is acetylated and is then nitrosated with nitrogen trioxide or nitrosyl chloride. The nitrosoacetyl amine thus obtained is then treated with an aromatic compound to get the biaryl derivative[32].



There are other methods which are either used for the preparation of some specific compound or are of

limited applicability. Amongst these may be mentioned the preparation of biphenyl from boiling chlorobenzene by the action of sodium[33] and the preparation of some biphenyl derivatives by the alkali fusion of fluorenones and sulphofluorenones[34].

Stereochemistry of biphenyls : An interesting feature of biphenyls which has stimulated a good deal of work in this field is the optical activity shown by some of the biphenyl derivatives due to molecular asymmetry. Christie and Kenner[35] reported in 1922 the resolution of 6,6′-dinitrodiphenic acid. Many similar compounds were later investigated by several other workers who found that generally compounds in which at least three of the four ortho positions are substituted with certain groups could be resolved. It was then soon found that two conditions are necessary for diphenyl compounds to exhibit optical activity (1) neither ring must have a vertical plane of symmetry. Thus (I) is not resolvable, but (II) is



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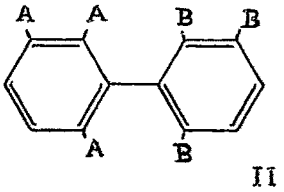
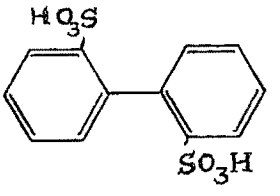


II

(2) The substituents in the ortho positions must have a large size so that they prevent the rings from becoming coplanar. The following compounds were resolved, 6-Nitrodiphenic acid, 6,6′-dinitrodiphenic acid, 6.6′-dichlorodiphenic acid and 2,2′-diamino-6,6′-dimethyldiphenyl.

In biphenyl the two benzene rings are co-axial, and in optically active diphenyl derivative, the rings are inclined to each other due to the spatial and repulsive effects of the groups in the ortho positions. The actual angle of inclination of the 2 rings depends on the nature of the substituent groups.

Diphenic acid is not optically active but Lesslie and Turner [36] resolved 2,2′-disulphonic acid (III) and the arsonium compound (IV). These groups are large enough to be impeded by ortho hydrogen atoms.



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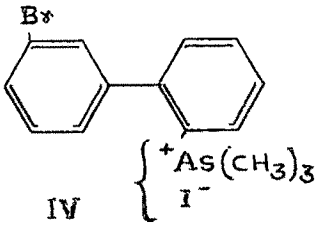
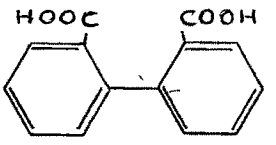


IV

The latter example is a unique one in that only one substituent in the ortho position produces optical activity in a diphenyl compound [37].

Diphenic acid is not optically active and its configuration is most probably (VI) . New Calculations show that the effective diameter of the carboxyl group is large enough to prevent configuration (V) from being coplanar and consequently if the two rings could be held more or less in this configuration the molecule could not be coplanar and hence would be resolvable.



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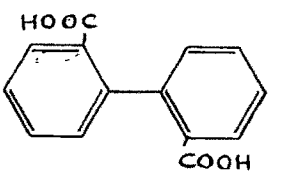
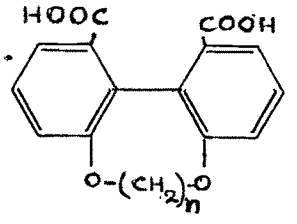
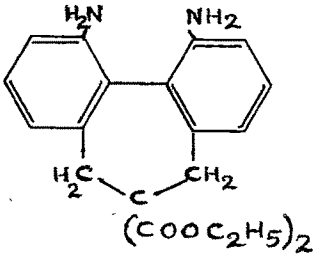


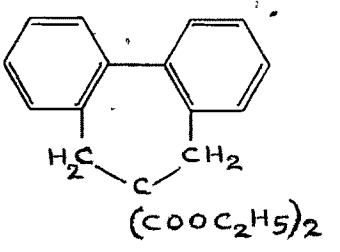
VI



VII



VIII



IX

Such a compound (VII) was prepared and resolved by Adams and Kornblum[38]. Iffland and Siegel[39] have also prepared the optically active diphenyl (VIII) which has a 2,2′-bridge and two amino groups in the 6,6′-position. These authors also prepared (IX) in optically active forms. This compound has the 2,2′-bridge but no substituents in the 6,6′-position.

Since the optical activity of diphenyl compounds arises from restricted rotation, it might be expected that racemisation of these compounds would not be possible. In practice, it has been found that many optically active biphenyl compounds can be racemised under suitable conditions eg. boiling in solution. The general theory of this racemisation is that heating increases the

amplitude of the vibration of the two benzene rings with respect to each other, thereby permitting the substituent groups to slip by one another.

Substitution in biphenyls :

Substitution in simple biphenyls gives rise to mono, di and tetra substituted biphenyl, the substitution taking place in the 2,4,2',4'-positions depending upon the reaction conditions and reagents used. The substitution in substituted biphenyls depends upon the substituent already present.

(a) Nitration : Biphenyl on nitration in cold acetic acid with conc. ntric acid gives 4-nitro- and 2-nitro-biphenyl[40], but when the nitration of biphenyl is carried out with conc. nitric acid in presence of sulphuric acid 2,2',4,4'-tetranitrobiphenyl is formed[41]. Buck and Thomson[42] studied the nitrations of biphenyl using both acetic anhydride and acetic acid as solvents under a variety of conditions. In acetic anhydride at -18°, a mean ortho and para ratio of 2.3 : 1 was obtained while nitration in acetic acid at 85-90° gave a mean ratio of 0.6 : 1 .

Hydroxybiphenyls on nitration give rise to different nitro derivatives depending upon the number of hydroxy groups and the reaction conditions. Borsche and Scholten[43] studied the nitration of 2-hydroxybiphenyl and isolated the 3,5-dinitro derivative. 3,3'-Dinitro derivative is the product when 4,4'-dihydroxybiphenyl is nitrated with

nitric acid at 0°C in acetic acid[44]. Methylation of one of the hydroxy groups reduces the activity as usual. Thus 4-methoxy-4′-hydroxybiphenyl with nitric acid in chloroform gives the 3′-nitro derivative whereas when the nitration is done with excess of nitric acid in chloroform it gives the 3,3′,5′-trinitro derivative[45]. Borsche and Scholten[43] have reported that 2,2′-dimethoxybiphenyl on warming with nitric acid in glacial acetic acid gives the 5,5′-dinitro derivative, but when first sulphonated and then nitrated with fuming nitric acid in presence of conc. sulphuric acid it gives the 3,3′,5,5′-tetranitro derivative.

Ethyl nitrate is found to be a stronger nitrating agent. In the nitration of 2,2′-dimethoxy-biphenyl with ethyl nitrate 3,3′,5,5′-tetranitro derivative is the product[46].

Nitration of 4,4′-dimethoxybiphenyl with nitric acid in chloroform at 60° or in acetic anhydride at 0°C gives the 3,3′-dinitro derivative which on further nitration gives the 3,3′,5,5′-tetranitro derivative[45] and 2,2′,6,6′-tetramethoxybiphenyl gives the 3,3′-dinitro derivative when the nitration is done with fuming nitric acid in acetic anhydride.[47]

Orientation of the nitro group in the nitration of alkyl biphenyls largely depends on the number and position of the alkyl groups. 3-Methylbiphenyl on nitration gives the 4-nitro or 4,4′-dinitro derivative

depending on the reaction conditions[48]. 4,4′-Dimethylbiphenyl gives the 3-nitro and 3,2′-dinitro derivative at ordinary temperature, but on heating the mixture to 50-55°, 2-nitro and 2,3′-dinitro derivative are formed.[49] When the methyl groups are replaced by ethyl groups in 4,4′-positions, the nitration is more smooth and 3,3′-dinitro derivative is the result[45]. Nitration of 2,4,6-trimethylbiphenyl at room temperature gives the 3,4′-dinitro derivative, but if the temperature is raised to 70-80° the 3,5,4′-trinitro derivative is formed[50].

Mascarelli and Gatti[51] have reported that in the nitration of 2-chlorobiphenyl the 4′-nitro and 3,4′-dinitro derivatives were formed. Similarly, 3,3′-dichlorobiphenyl on nitration with fuming nitric acid gives the 5,5′-dichloro-2,2′,4,4′-tetranitrobiphenyl. When the chlorine is in the 2,4- or 2,4′-positions the nitration takes place at the ortho or para positions with respect to the chlorine atom. Thus 4,4′-dichlorobiphenyl gives the 3,3′-dinitro derivative on nitration[52]. 3,3′,5,5′-Tetrachlorobiphenyl on nitration gives 2,2′- and 4,4′-dinitro derivative whereas 3,3′,4,4′-tetrachlorobiphenyl gives the 6,6′-dinitro compound which can be readily converted into 2,3,6,7-tetrachloro carbazole by reduction and cyclisation[53].

Bamus and Medrano[54] reported that the nitration of 4-bromobiphenyl with fuming nitric acid in the presence of sulphuric acid at 70-80° gave the 2′-nitro and 4′-nitro

2,4-dichloro or tetrachloro derivative (structure not assigned) respectively are the products.[65]

(ii) Bromination : Bromination of unsubstituted biphenyl or biphenyls with negative substituents requires catalysts such as phosphorous tribromide, ferric chloride or iron powder.[66] 4-Bromobiphenyl can be prepared by adding bromine to biphenyl in chloroform containing iron powder[67]. Berliner et al.[68] have reported the bromination of biphenyl to 4-bromobiphenyl along with a small amount of 2-and 3-bromobiphenyl.

Pentabromobiphenyl was obtained by adding bromine and chlorine to a mixture of biphenyl, carbon tetrachloride and powdered iron[69]. If the bromination of biphenyl is carried out with conc. sulphuric acid and bromine in presence of iron iodide as catalyst octabromo and decabromo biphenyls are the products.[70] Runeberg[71] has carried out the bromination of 2,2'-dihydroxybiphenyl with bromine in chloroform and acetic acid and obtained 5,5'-dibromo- and 3,3',5,5'-tetrabromo-biphenyl respectively. Yamashiro[72] has carried out the bromination of a number of nitro-hydroxybiphenyls and obtained mono, di and tribromo derivatives. Thus they prepared 3-bromo-5,5'-dinitro-, 3,3'-dibromo-5,5'-dinitro-, 3-bromo-3',5,5'-trinitro-, 5-bromo-3,5'-dinitro-, 3,5'-dibromo-3',5-dinitro-, 5-bromo-3,3',5'-trinitro-, 5-bromo-3,3',5-trinitro and 5,5'-dibromo-3,3'-dinitro-2,2'-dihydroxybiphenyl by the

bromination of the corresponding biphenyl derivatives.

Bromination of 2,2',6,6'-tetrachloro-4,4'-dihydroxybiphenyl gives an octabromo compound in which the bromine exchanges with chlorine even at -20°[63].

4-Methoxybiphenyl, on bromination with bromine in chloroform, gives the 4'-bromo derivative which on further bromination gives the 3,4'-dibromo derivative[73]. 4,4'-Dimethoxybiphenyl gives the 3,3'-dibromo derivative, but if the 4,4'-dimethoxybiphenyl is exposed to bromine vapours a tetrabromo derivative (structure not assigned) is formed[44]. Bromination of 3,3'-dimethoxybiphenyl gives the 6,6'-dibromo derivative[74]. 4-Methylbiphenyl[75] and 2,4,6-trimethylbiphenyl[50] on bromination gives the 4'-bromo and 3,5,4'-tribromo derivatives respectively.

Nitrobiphenyls react less readily in bromination but they can be brominated by using a catalyst. Thus 2-nitrobiphenyl in the presence of ferric chloride gives the 4'-bromo derivative and 3-nitrobiphenyl gives the 4'-bromo derivative[76].

Aminobiphenyls are easy to brominate. van Roosmalen[53] has reported the bromination of benzidine and 2,2'-dinitrobenzidine and obtained the 3,3',5,5'-tetrabromo derivatives. They also brominated

Boon-Long[86] failed to get 3,3′-diformyl-4,4′-dihydroxybiphenyl according to their method. Apsimon et al.[87] carried out the Gattermann formylation of 2,2′,4,4′-tetrahydroxybiphenyl and obtained the 5,5′-diformyl derivative.

(e) Fries rearrangement and Friedel-Crafts acylations : Fries rearrangement and Friedel-Crafts acylation have been extensively studied on various biphenyl derivatives by various workers and the work done has been reviewed in chapter IV of this thesis.

Miscellaneous reactions : Mercuration of 2,2′-dihydroxybiphenyl with mercuric acetate gives 2,2′-bis(acetoxymercuri)-3,3′,5,5′-tetrakis(acetoxymercuri) biphenyl and 2,2′-dihydroxy-x,x′-bis(acetoxymercuri) biphenyl. Similarly 4,4′-dihydroxybiphenyl also gives 4,4′-dihydroxy-3,3′-bis(acetoxymercuri) biphenyl and 4,4′-dihydroxy-3,3′,5,5′-tetrakis(acetoxymercuri)biphenyl[88,89].

Hazlet[90] has prepared the various sulphonic esters of 4,4′-dihydroxybiphenyl by treating the hydroxybiphenyl with benzene-, p-toluene-, o,m,p-nitrobenzene- and p-bromobenzene-sulphonyl chlorides.

Coupling reactions have been carried out on substituted 2,2′-dihydroxybiphenyl and dyes of various shades prepared[91]. Krasovitskii[92] has prepared various azodyes of 2,2′-dihydroxybiphenyl with amino group in the 4,4′-position. Anderson and Babigan[93] have prepared various azo dyes from 4,4′-dihydroxybiphenyl. Thus they

coupled this compound with diazotised amino salicylic acid, naphthionic acid, m-and p-phenetidine naphthyl amine β-sulphonic acid, anthranilic acid, o- and p-anisidine, o- and p-toluidine, p-bromoaniline, p-chloroaniline, metanilic acid, benzidine, 2-amino-toluidine-5-sulphonic acid, primuline and safranine and obtained dyes of various shades.

Dibenzofuran derivatives are formed when substituted 2,2'-diacetoxybiphenyls are mixed with 3-volumes of anhydrous alkaline carbonates or barium oxide, or lead monoxide or zinc oxide and heated at 200-10° for 0.5-2 hours[94]. The influence of substitution on the formation of a furan ring has been studied on 2,2'-dihydroxybiphenyl and its nitro, bromonitro and bromo derivatives[95].

Whalley and his co-workers[87] in their recent studies on the chemistry of fungi have carried out Pechmann condensation on 2,2',4,4'-tetrahydroxybiphenyl and obtained 6,6'-bicoumarinyl derivative.

The present work is a part of the systematic study of biphenyl derivatives undertaken in the laboratories here and deals with some studies on hydroxybiphenyl and their methyl ethers with a view to see if the reactions such as substitutions, rearrangements, condensations and cyclisations take place simultaneously in both the rings and to synthesise some heterocyclic compounds such as biflavonyls from biphenyl derivatives.

Chapter II deals with the chloromethylation of 2,2′,4,4′-tetrahydroxy-, 2,2′,4,4′-tetramethoxy-, 2,2′,5,5′-tetramethoxy- and 2,2′,6,6′-tetramethoxy-biphenyl and the conversion of these obtained chloromethyl derivatives into various other compounds.

Chapter III deals with the synthesis of biflavonyl derivatives through the condensation of formyl derivatives of hydroxybiphenyls with aromatic ketones and the cyclisation and dehydrogenation of the bichalconyls so obtained with selenium dioxide.

In chapter IV the Friedel-Crafts acetylation of some hydroxybiphenyls and their methyl ethers and the Fries migration of the acetoxy derivatives of biphenyls has been described.

Chapter V deals with the Beckmann rearrangement of the oximes of some C-acyl biphenyl derivatives and the synthesis of the amino derivatives required for comparison by the nitration of the biphenyl derivatives and the subsequent reduction of the nitro derivatives.

In the appendix, the synthesis of some biquinolyls is described.

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