CHAPTER II

CHLOROMETHYLATION OF SOME BIPHENYL DERIVATIVES

reduction it gives the methyl derivative.

Chloromethylation can also be accomplished by the use of chloromethyl ether (CH_3OCH_2Cl) or dichloromethyl ether (CH_2ClOCH_2Cl). The reaction often proceeds smoothly in the absence of a catalyst. Stannic chloride may be used as catalyst with less reactive compounds. Carbon disulphide or other indifferent solvents may be used as diluents. The chloromethyl ether is preferably used in excess and the reaction proceeds without hydrochloric acid and without any catalyst. Large number of aromatic hydroxy compounds and their alkyl ethers have been chloromethylated, but not much work appears to have been done on the chloromethylation of aromatic polyhydroxy compounds. This may be due to the very reactive nature of these compounds which gives rise to polymeric products instead of the expected chloromethyl derivatives.

Mndzhoyan and Aroyan[3] studied the effect of the alkoxy groups in chloromethylation. They chloromethylated anisole, phenetole, isopropyloxybenzene and butyloxybenzene and they found that the yield decreases according to the bulk of the group. While they could isolated the dichloromethyl derivative of anisole in 90 % yield, the butyloxybenzene gave only 48 % dichloromethyl derivative. Study of Profft and Drux[4] on chloromethylation of alkoxy benzene also leads to the same conclusion. While they could get the monochloromethyl derivative of phenetole in 71 % yield, the amyloxybenzene gave only 59 % monochloromethyl derivative.

Aromatic compounds with more than one ether group react vigorously as expected. Several alkoxy derivatives of hydroquinone were chloromethylated and the mono as well as the dichloromethyl derivatives were isolated[5]. However, the dimethyl ethers of resorcinol and catechol did not give pure products on chloromethylation. Negative groups in the polyalkoxy benzene retard the reaction considerably giving rise to chloromethyl derivatives in a satisfactory manner. For example, 2-bromo-4,5-dimethoxy benzylchloride was obtained from 3,4-dimethoxybromobenzene in good yield[6].

Mechanism : The exact mechanism of chloromethylation of benzene and other aromatics with formaldehyde and hydrogen chloride has not yet been elucidated. The previous reports[7,8] on the relative rate measurements for the chloromethylation of aromatic hydrocarbon show that the reaction appeared to involve an electrophilic attack on the aromatic nucleus. It seems to mean that the attacking species in the rate determining step is either $\overset{+}{C}H_2Cl$ or $\overset{+}{C}H_2OH$. The latter has been frequently suggested. The various works on the mechanism of this reaction have been summed up by Olah and Tolgyesi[2] and these are given below.

Ogato and Okano[9] studied the rate of chloromethylation of mesitylene in acetic acid containing 10 volumes of water at 60° by estimating the consumed formaldehyde iodimetrically and the consumed chloride ion. It was confirmed that mesityl carbinol and mesityl chloride are in mobile equilibrium under the experimental conditions. Their results are consistant with mechanism which involves a rate determining attack of protonated formaldehyde on mesitylene followed by the rapid reversible formation of the chloromethyl compound. In short they gave the mechanism as follows :

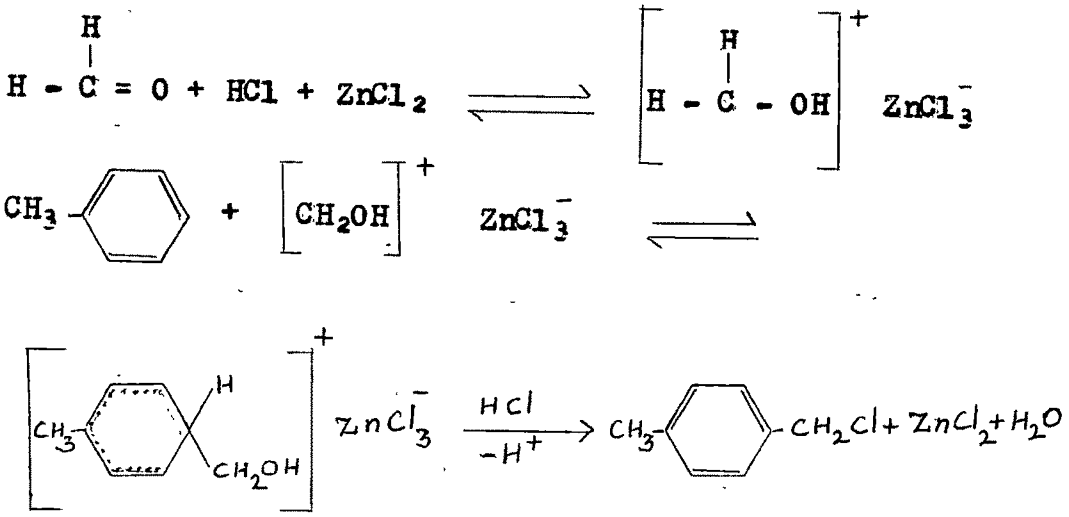
$$CH_2O + \overset{+}{H} \rightleftharpoons \overset{+}{C}H_2OH \text{ (mobile)}$$

$$ArH + \overset{+}{C}H_2OH \dashrightarrow ArCH_2OH + \overset{+}{H} \text{ (slow)}$$

$$ArCH_2OH + HCl \rightleftharpoons ArCH_2Cl + H_2O \text{ (mobile)}$$

The postulated mechanism explains the effect of the substituents on the rate, i.e. an electron releasing group in an aromatic nucleus facilitates the electrophilic attack by $\overset{+}{C}H_2OH$ while with the electron withdrawing group the reverse is true. The formation of diarylmethane or methylene bridged resins as byproduct is also applicable in terms of this scheme. According to this the attack of $\overset{+}{C}H_2Cl$ is improbable.

The same mechanism involving zinc chloride amd hydrochloric acid as catalysts can be written as follows:



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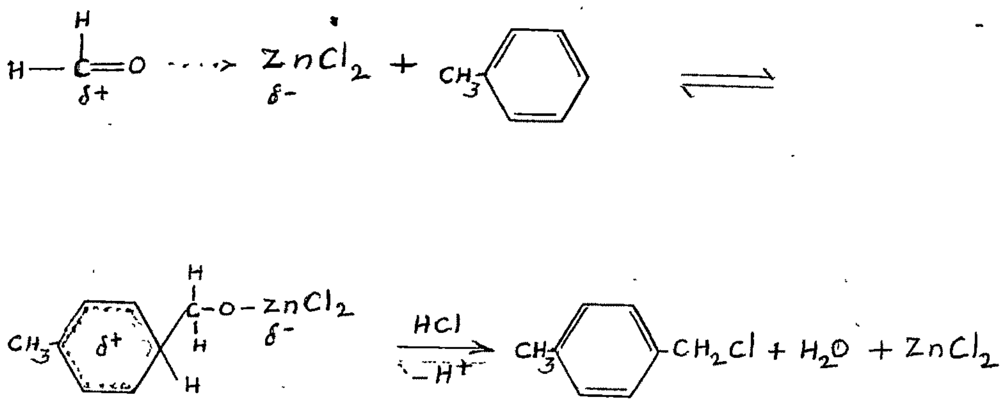


If the relatively stable carbonium ion, $HOCH_2^+$, is formed during the course of the reaction, the possible resonance with $HO^+=CH_2$ would be expected to greatly stabilize the intermediate ion and to facilitate its formation. Such an intermediate should exhibit relatively little steric hindrance for ortho-substitution and assumed high degree of resonance stabilization of the intermediate implies that the reaction would be highly selective.

Nazarov and Semenovsky[10], studying the mechanism of the halomethylation reaction, also came to this conclusion, namely that the active intermediate is the hydroxymethyl cation $\left[CH_2OH\right]^+$.

Another strong argument in favour of $\overset{+}{C}H_2OH$ mechanism of chloromethylation lies in the fact that chloromethylation gives the same isomer distribution as bromomethylation for a number of aromatic compounds. This indicates a common attacking species in both reactions.

If a halomethylation proceeded with the participation of halomethyl ions, then on stearic grounds, the bromomethylation of toluene, ethylbenzene etc. should result in ~~with~~ the formation of less ortho and more para isomer than the chloromethylation[11].

The work of Wadane, Trogus and Hess[12] reached in the same conclusion that the hydroxymethyl ion is the intermediate during chloromethylation. They established the following equilibria in acidic media.

pH	Equilibrium
below 2.6	$H_2C(OH)_2 \rightleftharpoons H_2\overset{+}{C} - OH + O\overset{-}{H}$
2.6-4.5	$H_2C(OH)_2 \rightleftharpoons H_2\overset{+}{C} - \bar{O} + \bar{O}H + \overset{+}{H}$
above 4.5	$H_2C(OH)_2 \rightleftharpoons H_2C(OH)\bar{O} + \overset{+}{H}$

The mechanism of chloromethylation using chloromethyl ethers in presence of zinc chloride is more complex under the acidic reaction conditions, it is possible that the dichloromethyl ethers undergo cleavage or hydrolysis with the formation of the same reactive species as in the case of chloromethylation with formaldehyde.

The role of catalysts, solvents and temperature :

A catalyst may or may not be required in chloromethylation. Catalysts which have been reported to be very useful are zinc chloride and acetic acid. Many other catalysts such as sulphuric acid, phosphoric acid and aluminium chloride are also used, though these catalysts tend to favour the formation of diarylmethane derivatives. In the chloromethylation of 5-nitro salicylaldehyde it is found that unless a large amount of anhydrous aluminium chloride is used as a catalyst no chloromethylation takes place[13].

Recently, Drechsler[14] has reported the use of zinc dust in place of zinc chloride as a catalyst in chloromethylation without any lowering of the yield. Thus he has chloromethylated benzene, toluene and benzyl chloride.

For liquids no diluent is required. Sometimes excess of the liquid itself acts as the solvent. For solids which do not dissolve in hydrochloric acid a solvent is used. Acetic acid, carbon disulphide, ethylene dichloride and dioxan are used as solvents.

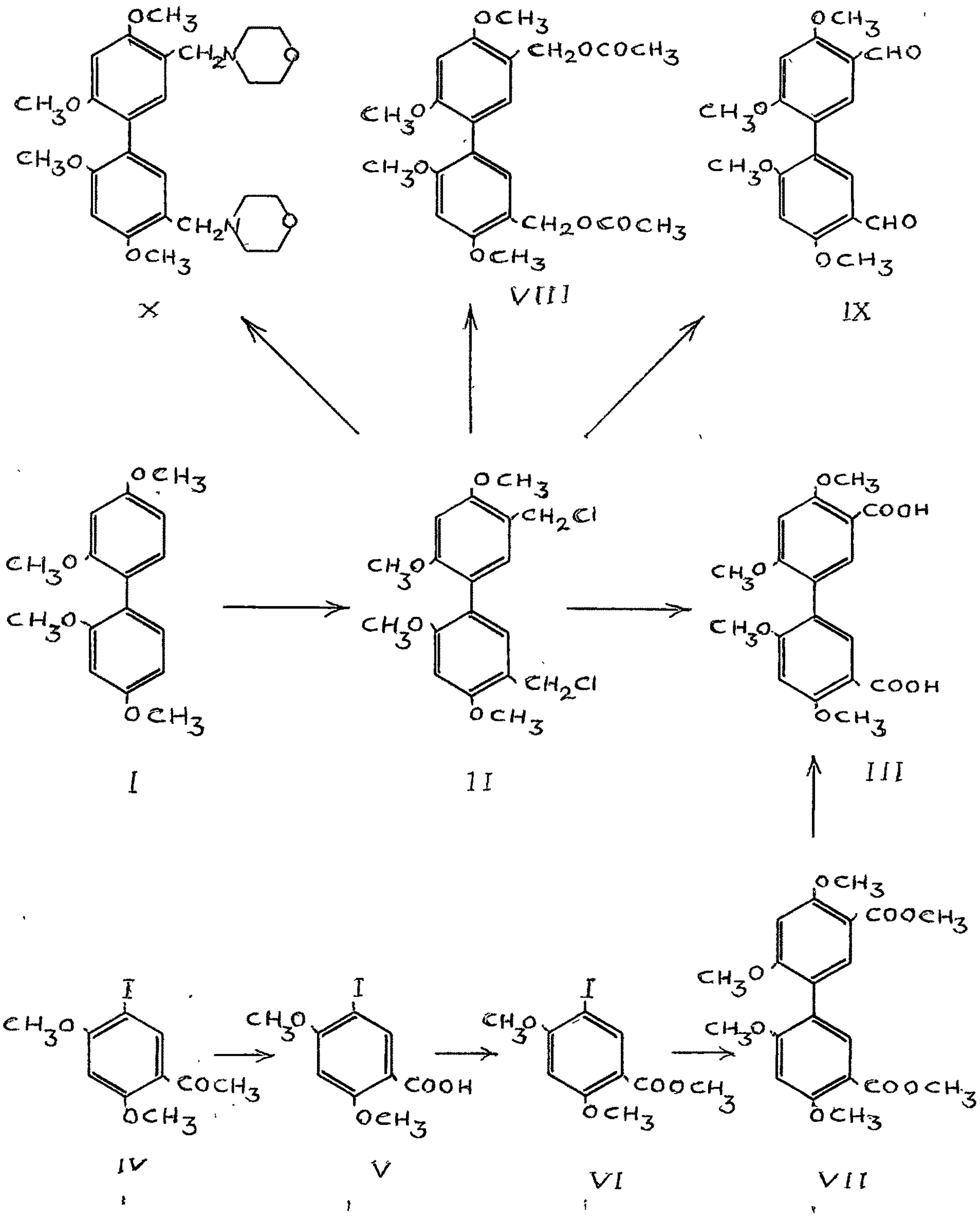
The rate of reaction also depends on the temperature of the reaction. A variety of reaction temperatures are used depending upon the type of compound to be chloromethylated. Highly reactive compounds react at room temparature or even at 0° while temperatures of $60\text{-}70^{\circ}$ are favoured for less reactive compounds. Sometimes reactions are carried out at 140° and under pressure.

Very little work has been done on the chloromethylation of biphenyl derivatives. Simple biphenyl has been chloromethylated and the 4-chloromethyl and 4,4′-dichloromethyl derivatives have been obtained[15]. 4-Methoxybiphenyl on chloromethylation gave the 3-chloromethyl derivative[16]. Quelet and Matarrasso[17] successfully chloromethylated 3,3′-dimethoxybiphenyl and 3,3′,4,4′-tetramethoxybiphenyl using dioxan as solvent and obtained the 6,6′-dichloromethyl derivatives in 80-90 % yield. They found that if the chloromethylation was carried out in acetic acid no pure product was obtained. Mathai and Sethna[18] studied the chloromethylation of 4,4′-dihydroxybiphenyl and 2,2′-dihydroxybiphenyl and their methyl ethers. They found that 4,4′-dihydroxybiphenyl on chloromethylation in dioxan and 4,4′-dimethoxybiphenyl on chloromethylation in acetic acid gave 3,3′-dichloromethyl derivatives in almost quantitative yields. Chloromethylation of 2,2′-dihydroxybiphenyl in acetic acid or dioxan at room temperature gave only a pasty mass from which no pure product could be isolated. 2,2′-Dimethoxybiphenyl on chloromethylation gave 5,5′-dichloromethyl derivative.

The present work deals with the chloromethylation of 2,2′,4,4′-tetramethoxybiphenyl, 2,2′,5,5′-tetramethoxybiphenyl and 2,2′,6,6′-tetramethoxybiphenyl.

Chloromethylation of 2,2′,4,4′-tetramethoxybiphenyl

2,2′,4,4′-Tetrahydroxybiphenyl on chloromethylation with paraformaldehyde in acetic acid or dioxan did not give a pure product. Therefore the chloromethylation of its tetramethyl ether was studied. 2,2′,4,4′-Tetramethoxybiphenyl (I) with excess of paraformaldehyde in acetic acid did not give a pure product but in dioxan, with excess of paraformadehyde, at 20°C, it afforded a di(chloromethyl) derivative (II) which on oxidation with alkaline potassium permanganate afforded 2,2′,4,4′-tetramethoxybiphenyl

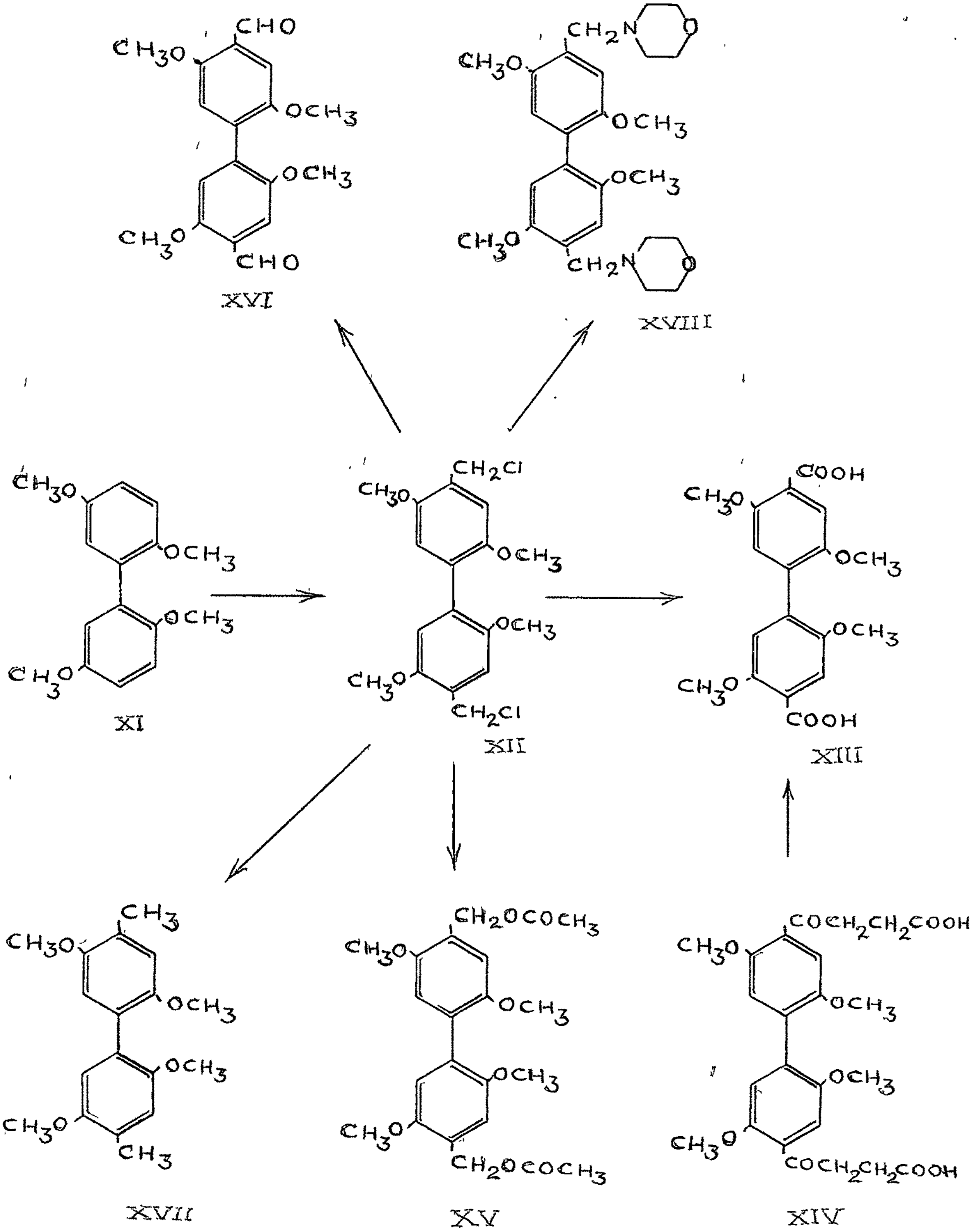

X
VIII
IX
I
II
III
IV
V
VI
VII

5,5'-dicarboxylic acid (III). This acid was synthesised for comparison as follows : 2,4-dimethoxy-5-iodo acetophenone (IV) prepared according to Shah and Sethna[19] was oxidised with alkaline potassium permanganate to 2,4-dimethoxy-5-iodo benzoic acid (V). This was esterified with dimethyl sulphate in acetone and the ester (VI) obtained subjected to Ullmann reaction. Dimethyl 2,2',4,4'-tetramethoxybiphenyl-5,5'-dicarboxylate (VII) so obtained when hydrolysed with alkali gave the dicarboxylic acid (III) described above.

On heating with acetic anhydride in presence of fused sodium acetate the di-(chloromethyl) derivative (II) gave 2,2',4,4'-tetramethoxy-5,5'-diacetoxymethylbiphenyl (VIII) and when heated with hexamine in chloroform it gave 2,2',4,4'-tetramethoxy-5,5'-diformylbiphenyl (IX) which was characterised by the formation of the di-(2,4-dinitrophenylhydrazone) derivative. The di-(chloromethyl) derivative (II) on reaction with morpholine gave the corresponding Mannich base (X).

Chloromethylation of 2,2',5,5'-tetramethoxybiphenyl

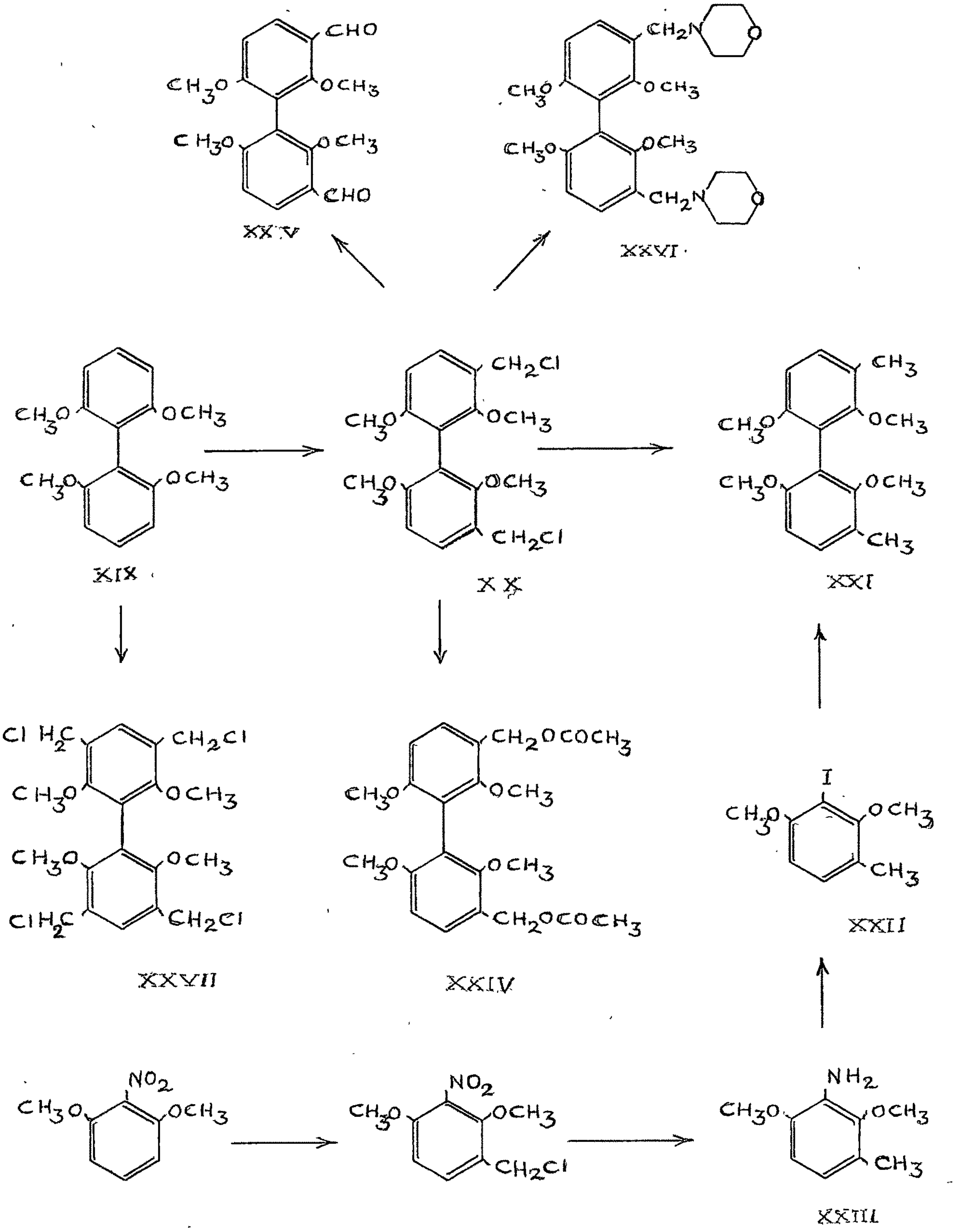
2,2',5,5'-Tetramethoxybiphenyl (XI) gave a di-(chloromethyl) derivative (XII) with excess of paraformaldehyde and hydrogen chloride in glacial acetic acid at room temperature. The di-(chloromethyl) derivative (XII) on oxidation with alkaline potassium permanganate provided the known 2,2',5,5'-tetramethoxybiphenyl-4,4'-dicarboxylic acid (XIII) as seen by direct comparison with the


CHO
CH3O
OCH3
OCH3
CH3O
CHO
XVI
CH2N
O
CH3O
OCH3
OCH3
CH3O
CH2N
O
XVIII
CH3O
OCH3
OCH3
CH3O
XI
CH2Cl
CH3O
OCH3
OCH3
CH3O
CH2Cl
XII
COOH
CH3O
OCH3
OCH3
CH3O
COOH
XIII
CH3
CH3O
OCH3
OCH3
CH3O
CH3
XVII
CH2OCOCH3
CH3O
OCH3
OCH3
CH3O
CH2OCOCH3
XV
COCH2CH2COOH
CH3O
OCH3
OCH3
CH3O
COCH2CH2COOH
XIV

Product obtained according to Brockmann and Vorbrueggen[20] who obtained this acid by the oxidation of 2,2',5,5'-tetramethoxy-4,4'-bis-(β-carboxy propionyl) biphenyl (XIV) with sodium hypobromite. The diacetoxymethyl derivative (XV) was prepared by refluxing the di-(chloromethyl) derivative (XII) with acetic anhydride and sodium acetate. Sommelet reaction on the di-(chloromethyl) derivative (XII) gave the 2,2',5,5'-tetramethoxy-4,4'-diformylbiphenyl (XVI) which was characterised by the formation of the di-(2,4-dinitrophenylhydrazone) derivative. The di-(chloromethyl) derivative (XII) when subjected to reduction in dioxan with zinc and hydrochloric acid afforded 2,2',5,5'-tetramethoxy-4,4'-dimethylbiphenyl(XVII). The di-(chloromethyl) biphenyl (XII) on reaction with morpholine gave the corresponding Mannich base (XVIII).

Chloromethylation of 2,2',6,6'-tetramethoxybiphenyl

2,2',6,6'-Tetramethoxybiphenyl (XIX) on chloromethylation with excess of paraformaldehyde in acetic acid at room temperature gave 3,3'-di-(chloromethyl) biphenyl (XX) which on reduction with zinc and hydrochloric acid yielded the 3,3'-dimethylbiphenyl derivative(XXI). This was confirmed by direct comparison with the product obtained through the Ullmann reaction on 2,4-dimethoxy-3-iodotoluene (XXII) which in turn was prepared by the Sandmeyer $ reaction on diazotised 2,6-dimethoxy-3-methyl aniline (XXIII) according to Mathai and Sethna[18]. The diacetoxy derivative (XXIV) was prepared by refluxing the


XXV
XXVI
XIX
XX
XXI
XXVII
XXIV
XXII
XXIII

di-(chloromethyl) derivative (XX) with acetic anhydride and sodium acetate on a steam bath for 2 hours. The di-(chloromethyl) derivative (XX) was subjected to Sommelet reaction and the 3,3′-diformyl derivative (XXV) obtained. This was characterised by the preparation of its di-(2,4-dinitrophenylhydrazone). The di-(chloromethyl) biphenyl (XX) on reaction with morpholine gave the corresponding Mannich base (XXVI).

Another product was isolated from the reaction mixture in the above chloromethylation, the analysis of which agreed with a tetra-(chloromethyl) derivative (XXVII). 3,3′,5,5′-Tetra-(chloromethyl) structure has been tentatively assigned to the product as this appears to be the only possible structure.

EXPERIMENTAL

Chloromethylation of 2,2',4,4'-tetramethoxybiphenyl :

2,2',4,4'-Tetramethoxy-5,5'-di(chloromethyl)biphenyl :

Paraformaldehyde (1.2 g. ; 0.03 M) was taken in dioxan (10 ml.) and saturated with dry hydrogen chloride at 20°. 2,2',4,4'-Tetramethoxybiphenyl (2.74 g. ; 0.01 M) was then added and the hydrogen chloride gas was passed for further 10 minutes. The reaction mixture turned green. It was kept overnight and the product which separated was then filtered and crystallised from xylene, m.p. 190°. Yield 2.1 g.

Analysis : Found : C,58.0 % ; H,5.2 % ; Cl,18.7 %.
$C_{18}H_{20}O_4Cl_2$ requires : C,58.2 % ; H,5.4 % ; Cl,19.1 %.

2,2',4,4'-Tetramethoxybiphenyl-5,5'-dicarboxylic acid :

The above di(chloromethyl) derivative (0.5 g.) was refluxed with potassium permanganate (2 g.) and sodium hydroxide (10 % ; 10 ml.) for 1 hour. The reaction mixture was filtered hot and the excess of potassium permanganate was decomposed with sodium bisulphite. The filtrate was then acidified. The precipitated acid after purification by bicarbonate treatment was crystallised from ethanol, m.p. 255°.

Analysis : Found : C,59.5 % ; H,4.2 %.
$C_{18}H_{18}O_8$ requires : C,59.6 % ; H,4.6 %.

The same acid was prepared for comparison as follows :

2,4-Dimethoxy-5-iodobenzoic acid :

2,4-Dimethoxy-5-iodoacetophenone[19] (2 g.) was suspended in sodium hydroxide (20 ml. ; 20 %) and potassium permanganate (6 g.) was added. The mixture was gently refluxed on a wire gauze for 1 hour. The product obtained on working up as before crystallised from dilute acetic acid, m.p. 210°.

Analysis : Found : C,34.9 % ;H,2.8 % ; I,41.2 %.

$C_9H_9O_4I$ requires : C,35.1 % ;H,2.9 % ; I,41.2 %.

Methyl-2,4-dimethoxy-5-iodobenzoate :

2,4-Dimethoxy-5-iodobenzoic acid (1 g.) was dissolved in acetone (10 ml.) and dimethyl sulphate (1 ml.) and anhydrous potassium carbonate (3 g.) was added. The mixture was refluxed for 2 hours on a steam bath and then poured in water. The separated product was filtered and crystallised from benzene,m.p.120°.

Analysis : Found : C,37.4 % ; H,3.8 % ; I,39.1 %.

$C_{10}H_{11}IO_4$ requires : C,37.2 % ; H,3.4 % ; I,39.4 %.

Dimethyl-2,2′,4,4′-tetramethoxybiphenyl-5,5′-dicarboxylate :

A mixture of methyl-2,4-dimethoxy-5-iodobenzoate (1 g.) and copper bronze (2 g.) was heated in an oil bath at 225-30° for 2 hours. The mixture was extracted with benzene and the product obtained was crystallised from benzene, m.p. 200°.

Analysis : Found : C,61.5 % ; H,5.7 %.

$C_{20}H_{22}O_8$ requires : C,61.5 % ; H,5.4 %.

Hydrolysis :

The above ester (0.3 g.) dissolved in methanol was hydrolysed by heating with sodium hydroxide (10 % ; 10 ml.) for 1 hour. The product obtained on acidification crystallised from ethanol, m.p.255°. Mixed m.p. with 2,2′,4,4′-tetramethoxybiphenyl-5,5′-dicarboxylic acid described above was not depressed.

2,2′,4,4′-Tetramethoxy-5,5′-diacetoxymethylbiphenyl :

The di-(chloromethyl) derivative (0.5 g.) was heated with acetic anhydride (5 ml.) and fused sodium acetate (2 g.) for 2 hours. on a steam bath. The reaction mixture was poured into water and the product obtained crystallised from benzene, m.p. 130°.

Analysis : Found : C,63.3 % ; H, 6.5 %.

$C_{22}H_{26}O_8$ requires : C,63.2 % ; H,6.2 %.

2,2′,4,4′-Tetramethoxy-5,5′-diformylbiphenyl :

The 5,5′-dichloromethyl derivative (1 g.) was refluxed with hexamethylenetetramine (6 g.) in chloroform (30 ml.) on a steam bath for 2 hours. The complex product which separated was decomposed with dilute acetic acid by refluxing on a wire gauze for 30 minutes. The product separating on cooling was crystallised from acetic acid , m.p. 245°.

Analysis : Found : C,65.4 % ; H,5.6 %.

$C_{18}H_{18}O_6$ requires : C,65.5 % ; H,5.5 %.

Apsimon et al.[21] who prepared this compound recently by a different method, reported m.p. 238°.

The di-(2,4-dinitrophenylhydrazone):

Prepared by heating a mixture of the above diformyl derivative in alcohol and 2,4-dinitrophenylhydrazine hydrochloride in alcohol on a steam bath for 30 minutes. The hydrazone ~~separated~~ was crystallised from nitrobenzene. It decomposed above 300°.

Analysis : Found : N, 16.6 %.
$C_{30}H_{26}O_{12}N_8$ requires : N, 16.2 %.

2,2′,4,4′-Tetramethoxy-5,5′-di-(morpholinomethyl)biphenyl :

2,2′,4,4′-Tetramethoxy-5,5′-di-(chloromethyl) biphenyl (0.5 g.) was dissolved in minimum quantity of benzene and morpholine (2 ml.) was added. The reaction mixture was refluxed on a steam bath for 2 hours. Benzene was removed and the product crystallised from benzene-petroleum ether, m.p. 156°.

Analysis : Found : N, 6.0 %.
$C_{26}H_{36}N_2O_6$ requires : N, 5.9 %.

Chloromethylation of 2,2′,5,5′-tetramethoxybiphenyl:

2,2′,5,5′-Tetramethoxy-4,4′-di-(chloromethyl)biphenyl :

Paraformaldehyde (1.2 g.; 0.03 M) in acetic acid (15 ml.) was saturated with dry hydrogen chloride and 2,2′,5,5′-tetramethoxybiphenyl (2.74 g. ; 0.01 M) was added and the reaction mixture kept overnight. The separated product was filtered and crystallised from xylene in colourless needles, m.p. 192°. Yield 2.8 g.

Analysis : Found : C,58.1 % ; H,5.0 % ; Cl,18.9 %.
$C_{18}H_{20}Cl_2O_4$ requires : C,58.2 % ; H,5.4 % ; Cl,19.1 %.

2,2',5,5'-Tetramethoxybiphenyl-4,4'-dicarboxylic acid :

A mixture of 2,2',5,5'-tetramethoxy-4,4'-di-(chloromethyl)biphenyl (0.5 g.), sodium hydroxide (10 ml. ; 10 %) and potassium permanganate (2 g.) was heated gently on a wire gauze for 1 hour and then filtered. The excess of potassium permanganate was decomposed with sodium bisulphite and the filtrate on acidification gave the 4,4'-dicarboxylic acid which was purified through the bicarbonate and then crystallised from ethanol, m.p. 255°.

Analysis : Found : C,59.2 % ; H,4.3 %.
$C_{18}H_{18}O_8$ requires : C,59.6 % ; H,4.6 %.

The same acid was prepared for comparison as follows : 2,2',5,5'-tetramethoxy-4,4',bis-(β-carboxypropionyl) biphenyl (0.5 g.) prepared by the succinoylation of 2,2',5,5'-tetramethoxybiphenyl according to Brockmann and Vorbrueggen[20] was refluxed with potassium permanganate (4 g.) and sodium hydroxide (20 ml. ; 10 %) for 30 minutes. The product obtained on working up as usual crystallised from ethyl alcohol, m.p. 255°. Mixed m.p. with the acid described above was not depressed. Brockmann and Vorbrueggen[20] reported m.p. 244-46°.

2,2',5,5'-Tetramethoxy-4,4'-diacetoxymethylbiphenyl :

Prepared from 4,4'-di-(chloromethyl)derivative, by refluxing with acetic anhydride and fused sodium acetate, was crystallised from benzene in colourless needles, m.p. 169-70°.

Analysis : Found : C, 63.4 % ; H, 6.1 %.
$C_{22}H_{26}O_8$ requires : C, 63.2 % ; H, 6.2 %.

2,2′,5,5′-Tetramethoxy-4,4′-diformylbiphenyl :

The 4,4′-di-(chloromethyl) derivative (1 g.) was refluxed with hexamine (6 g.) in chloroform (30 ml.) for 2 hours and the complex obtained was decomposed with dilute acetic acid by heating gently on a wire gauze for 2 hours. The product separating on cooling was crystallised from acetic acid in yellow needles, m.p.237°.

Analysis : Found : C, 65.1 % ; H, 5.2 %.
$C_{18}H_{18}O_6$ requires : C, 65.5 % ; H, 5.5 %.

The di-(2,4-dinitrophenylhydrazone) :

Prepared as usual and crystallised from nitrobenzene gave m.p. > 325°.

Analysis : Found : N, 16.5 %.
$C_{30}H_{24}O_{12}N_8$ requires : N, 16.2 %.

2,2′,5,5′-Tetramethoxy-4,4′-dimethylbiphenyl :

2,2′,5,5′-Tetramethoxy-4,4′-di-(chloromethyl) biphenyl was dissolved in dioxan and zinc dust (2 g.) was added. This was followed by hydrochloric acid (Conc.5 ml.) portionwise. The reaction mixture after heating for 1 hour on a steam bath was filtered. The filtrate on dilution provided the dimethyl derivative.

It was crystallised from ethyl alcohol, m.p. 130°.

Analysis : Found : C, 71.8 % ; H, 7.2 %.
$C_{18}H_{22}O_4$ requires : C, 71.5 % ; H, 7.3 %.

Fitcher[22], who prepared the same compound by a different method, reported m.p. 135°.

2,2',5,5'-Tetramethoxy-4,4'-di-(morpholinomethyl)biphenyl :

2,2',5,5'-Tetramethoxy-4,4'-di-(chloromethyl) biphenyl (0.5 g.) was dissolved in minimum quantity of benzene and morpholine (2 ml.) was added and the reaction mixture heated for 2 hours on a steam bath. Benzene was removed and the product obtained crystallised from benzene-petroleum ether, m.p. 156°.

Analysis : Found : N, 6.1 %.
$C_{26}H_{36}N_2O_6$ requires : N, 5.9 %.

Chloromethylation of 2,2',6,6'-tetramethoxybiphenyl :

2,2',6,6'-Tetramethoxy-3,3'-di-(chloromethyl)biphenyl :

Dry hydrogen chloride gas was passed through paraformaldehyde (1.2 g. ; 0.03 M) in acetic acid (15 ml.) at room temperature till the paraformaldehyde dissolved and 2,2',6,6'-tetramethoxybiphenyl (2.74 g. ; 0.01 M) was then added. The product separating on keeping overnight was crystallised from benzene in colourless cubes. M.p. 200° (decomp.). Yield 2.5 g.

Analysis : Found : C, 58.4 %; H, 5.7 %; Cl, 19.0 %.
$C_{18}H_{20}O_4Cl_2$ requires : C, 58.2 %; H, 5.4 %; Cl, 19.1 %.

2,2',6,6'-Tetramethoxy-3,3',5,5'-tetra-(chloromethyl)biphenyl :

After removing the 3,3'-di-(chloromethyl)biphenyl from the above reaction mixture, the filtrate was poured in water and the separated product was crystallised from petroleum ether in colourless plates, m.p.110°.
Yield 0.5 g.

Analysis : Found : C,51.0 % ; H,4.3 % ; Cl,30.0 %.
$C_{20}H_{22}O_4Cl_4$ requires : C,51.3 % ; H,4.7 % ; Cl,30.3 %.

2,2',6,6'-Tetramethoxy-3,3'-dimethylbiphenyl :

2,2',6,6'-Tetramethoxy-3,3'-di-(chloromethyl) biphenyl (0.5 g.) was dissolved in dioxan and zinc dust (2 g.) was added. This was followed by conc.hydrochloric acid in small lots. The mixture was refluxed on a steam bath for 1 hour. It was then filtered and the filtrate on dilution provided the dimethyl derivative. It was crystallised from light petroleum in cubes,m.p.101°.

Analysis : Found : C, 71.6 % ; H,7.5 %.
$C_{18}H_{22}O_4$ requires : C, 71.5 % ; H,7.3 %.

The same dimethyl derivative was prepared by another method for comparison as follows :

2,4-Dimethoxy-3-iodotoluene :

2,6-Dimethoxy-3-methylaniline was prepared by the chloromethylation and reduction of 2,6-dimethoxynitrobenzene according to Mathai and Sethna[18]. 2,6-Dimethoxy-3-methylaniline (2 g.) dissolved in hydrochloric acid (1:1 ; 15 ml.) was cooled below 5° and sodium nitrite solution (1 g. in 5 ml. water) was added portionwise. The reaction mixture was kept for 30 minutes below 5°. Potassium iodide (4 g. in 10 ml. water) was added to it and the mixture was kept for 1 hour at room temperature. It was then heated on a steam bath for 1 hour and the product separating on cooling was filtered and crystallised from light petroleum, m.p. 86°.

Analysis : Found : C,38.7 %; H,3.7 % ; I,45.6 %.
$C_9H_{11}IO_2$ requires : C,38.8 %; H,4.0 % ; I,45.7 %.

Ullmann reaction :

The above iodo derivative (1 g.) mixed with copper bronze (2 g.) was heated in an oil bath at 225-35° for 2 hours. The reaction product was extracted with benzene and crystallised from light petroleum, m.p. 101°. Mixed m.p. with 2,2′,6,6′-tetramethoxy-3,3′-dimethylbiphenyl described above was not depressed.

2,2′,6,6′-Tetramethoxy-3,3′-diacetoxymethylbiphenyl :

It was prepared by refluxing the 3,3′-di-(chloromethyl) derivative with acetic anhydride and fused sodium acetate. The product obtained on pouring the reaction mixture in water crystallised from benzene, m.p. 114°.

Analysis : Found : C, 63.1 % ; H, 6.1 %.
$C_{22}H_{26}O_8$ requires : C, 63.2 % ; H, 6.2 %.

2,2′,6,6′-Tetramethoxy-3,3′-diformylbiphenyl :

The 3,3′-di-(chloromethyl) derivative (1 g.)

was dissolved in chloroform (30 ml.), hexamine (6 g.) was added and the mixture was refluxed on a steam bath for 2 hours. The separated complex was filtered and refluxed with dilute acetic acid for 2 hours. On cooling, the formyl derivative separated. It crystallised from ethyl alcohol in colourless needles, m.p. 152°.

Analysis : Found : C, 65.8 % ; H, 5.4 %.

$C_{18}H_{18}O_6$ requires : C, 65.5 % ; H, 5.5 %.

The di-(2,4-dinitrophenylhydrazone) :

Prepared as usual and crystallised from nitrobenzene gave m.p. 290-91°.

Analysis : Found : N, 15.9 %.

$C_{30}H_{24}N_8O_{12}$ requires : N, 16.2 %.

2,2',6,6'-Tetramethoxy-3,3'-di-(morpholinomethyl)biphenyl :

2,2',6,6'-Tetramethoxy-3,3'-di-(chloromethyl)biphenyl (0.5 g.) was dissolved in minimum quantity of toluene and morpholine (2 ml.) was added. The reaction mixture was refluxed for 2 hours. Toluene was evaporated and the product obtained crystallised from benzene-petroleum ether, m.p. 116°.

Analysis : Found : N, 6.2 %.

$C_{26}H_{36}N_2O_6$ requires : N, 5.9 %.

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