CHAPTER IV

Chloromethylation of 4,4'- and 2,2'-dimethoxydiphenyl methane :

The replacement of a hydrogen atom, generally of an aromatic compound and in some aliphatic compounds by a chloromethyl group is known as chloromethylation. The reaction can be carried out most conveniently by the interaction of formaldehyde or its polymer such as paraformaldehyde, and hydrogen chloride. Chloromethyl ether and chloromethyl sulfide are also used as chloromethylating agents.

Blanc[1,2] demonstrated the wide scope of the reaction and hence it is commonly referred to as the Blanc reaction.

Fuson and McKeever[3] have reviewed the work on chloromethylation until 1941. A more recent review is by Olah and Tolgyesi[4].

This reaction has great synthetic importance as the chlorine atom of the chloromethyl group can be replaced by hydroxy, cyano, methoxy, acetoxy or other groups by treating with appropriate reagents. Moreover, chloromethyl derivatives can be converted into a formyl derivative by the Sommelet reaction and the formyl derivative can then be used for further synthetical work. The chloromethyl derivative is conveniently converted into the corresponding acid by oxidation and on reduction it yields the methyl derivative.

When condensed with amines, the chloromethyl derivatives give aminomethyl derivatives, which have pronounced physiological action such as central nervous system stimulation.

Electron donating groups such as hydroxyl, alkyl and alkoxy enhance the reaction rate and the reaction proceeds even in the absence of a catalyst to form the chloromethyl derivative in good yield. The reaction has been applied to a wide variety of aromatic and heterocyclic compounds.

Electron withdrawing substituents either by inductive or mesomeric effect, retard the rate of the reaction. Halogens by way of their negative inductive effect deactivate the nucleus. However, halobenzenes readily undergo chloromethylation and give good yields when the reaction is carried out using drastic conditions[5]. The presence of electron donating groups, however, counteracts the influence of the negative substituents and many examples of this reaction have been reported as in the case of alkylated halobenzenes[3].

The various views on the mechanism of chloromethylation have been summarised by Olah and Tolgyesi[4].

A large number of procedures have been adopted for chloromethylation. Formaldehyde can be applied in the form of formalin, paraformaldehyde or trioxymethylene. Chloromethyl ether and chloromethyl sulfide are equally effective chloromethylating agents.

A catalyst may or may not be required. The catalysts used in chloromethylation include both Lewis acid type halides and proton acids. Acidic halide catalysts used in chloromethylation include zinc chloride[1,6], a mixture of zinc chloride and aluminium chloride[7], stannic chloride[8], antimony trichloride[9] and boron phosphate[10]. The most widely used proton acid catalysts are hydrochloric acid[11,12], sulfuric acid[13,14], phosphoric acid[15,16], a mixture of acetic acid and chlorosulfonic acid and acetic acid. Catalysts which are used most frequently are zinc chloride and acetic acid. The latter also acts as a solvent. Solvents frequently used are diethyl ether, dioxan, dimethoxy methane, carbon tetrachloride, chloroform, carbon disulfide and benzene.

The rate of the reaction also depends upon the temperature of the reaction. Highly reactive compounds react at room temperature or even at 0° while temperatures of 60-70° are much favoured for less reactive compounds. Sometimes the reactions are carried out at 140° under pressure.

Present work : The present work deals with the chloromethylation of 2,2'- and 4,4'-dihydroxydiphenyl methane, their methyl ethers and 4,4'-dihydroxydiphenyl sulfone.

Biphenyl was chloromethylated by Braun et al.[17] who obtained 4-chloromethyl- and 4,4'-di(chloromethyl)biphenyl. 4-Methoxybiphenyl on chloromethylation gave the 3-chloromethyl derivative[18]. Quelet and Matarrasso[19] successfully chloromethylated 3,3'-dimethoxybiphenyl and 3,3', 4,4'-tetramethoxybiphenyl using dioxan as solvent and obtained the 6,6'-di(chloromethyl) derivatives. Mathai and Sethna[20] studied the chloromethylation of 2,2'- and 4,4'-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'-di(chloromethyl) derivatives. 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'-di(chloromethyl) derivative.

Kanakalakshmi, Mathai and Sethna[21] studied the chloromethylation of 2,2'-, 4,4'-, 2,2',5,5'- and 2,2',6,6'-tetramethoxybiphenyls in dioxan or acetic acid medium and obtained the 5,5'-di(chloromethyl)-, 4,4'-di(chloromethyl)- and 3,3'-di(chloromethyl) derivatives respectively.

Benzophenone does not undergo chloromethylation but Fuson and McKeever[22] successfully chloromethylated 2,4,6-trimethylbenzophenone and obtained the 3-chloromethyl derivative. Balani and Sethna[23] chloromethylated 4-hydroxybenzophenone and its methyl ether and obtained the 3-chloromethyl derivative. They have also carried out the chloromethylation of 2,2'-dihydroxybenzophenone and 2,2'-dimethoxybenzophenone[24], 4,4'-dihydroxy- and 4,4'-dimethoxybenzophenone[25], 2,4-dihydroxy- and 2,4-dimethoxybenzophenone[24]. In all the above cases hydroxybenzophenones did not give a pure product but their methoxy derivatives give the 5,5'-di(chloromethyl), 3,3'-di(chloromethyl) and 5-chloromethyl derivatives respectively.

Maquin[26,27] chloromethylated diphenyl methane successfully and obtained 4-chloromethyl- and 4,4'-di-(chloromethyl)diphenyl methane. Szmant and Dudek[28] have chloromethylated diphenyl sulfide and obtained the chloromethyldiphenyl sulfide. No work appears to have been done on chloromethylation of hydroxy and methoxy derivatives of diphenyl methane and diphenyl sulfone. It was therefore thought of interest to study the chloromethylation of dihydroxy and dimethoxy derivatives of diphenyl methane and diphenyl sulfone and to use the chloromethyl derivatives obtained for further synthesis.

Chloromethylation of 4,4'-dimethoxydiphenyl methane :

Chloromethylation of 4,4'-dihydroxydiphenyl methane with two or more moles of formaldehyde gave a polymeric product even at low temperatures, and no pure product could be isolated.

However, chloromethylation of 4,4'-dimethoxydiphenyl methane with two or more moles of formaldehyde in acetic acid (90 %) at room temperature gave a di(chloromethyl) derivative (I) in good yield. The above di(chloromethyl) derivative on oxidation with alkaline potassium permanganate gave the known 4,4'-dimethoxybenzophenone-3,3'-diearboxylic acid (II) m.p. 245°, identical with the acid obtained by Balani and Sethna[25] by the oxidation of 3,3'-diacetyl-4,4'-dimethoxybenzophenone. Ishiwata and Takada[29] have prepared the same acid by the oxidation of 3,3'-diformyl-4,4'-dimethoxydiphenyl methane and have reported the m.p. 242-43°.

The dichloromethyl derivative on refluxing with sodium acetate and acetic anhydride gave the di(acetoxymethyl) derivative (III). The 3,3'-di(cyanomethyl) derivative (IV) was obtained by treatment with potassium cyanide. This was hydrolysed with conc. hydrochloric acid to the corresponding 3,3'-di(carboxymethyl) derivative (V). The 3,3'-di(chloromethyl) derivative on Sommelet reaction gave the 3,3'-diformyl derivative (VI). On demethylation it gave 3,3'-diformyl-4,4'-dihydroxydiphenyl methane (VII), previously prepared by Marvel and Tarkoy[30] by the condensation of salicylaldehyde with trioxan. On reduction with zinc and acetic acid the di(chloromethyl) derivative did not give any pure product.

The diformyl derivative (VI) was condensed with hippuric acid in presence of acetic anhydride and sodium acetate to give the diazlactone derivative(VIII). Attempt to synthesise the di-α-aminoacid derivative (IX) by refluxing with hydriodic acid and acetic anhydride in presence of red phosphorus did not succeed. The aminoacid could not be isolated.

<u>Chloromethylation of 2,2'-dimethoxydiphenyl methane</u> :

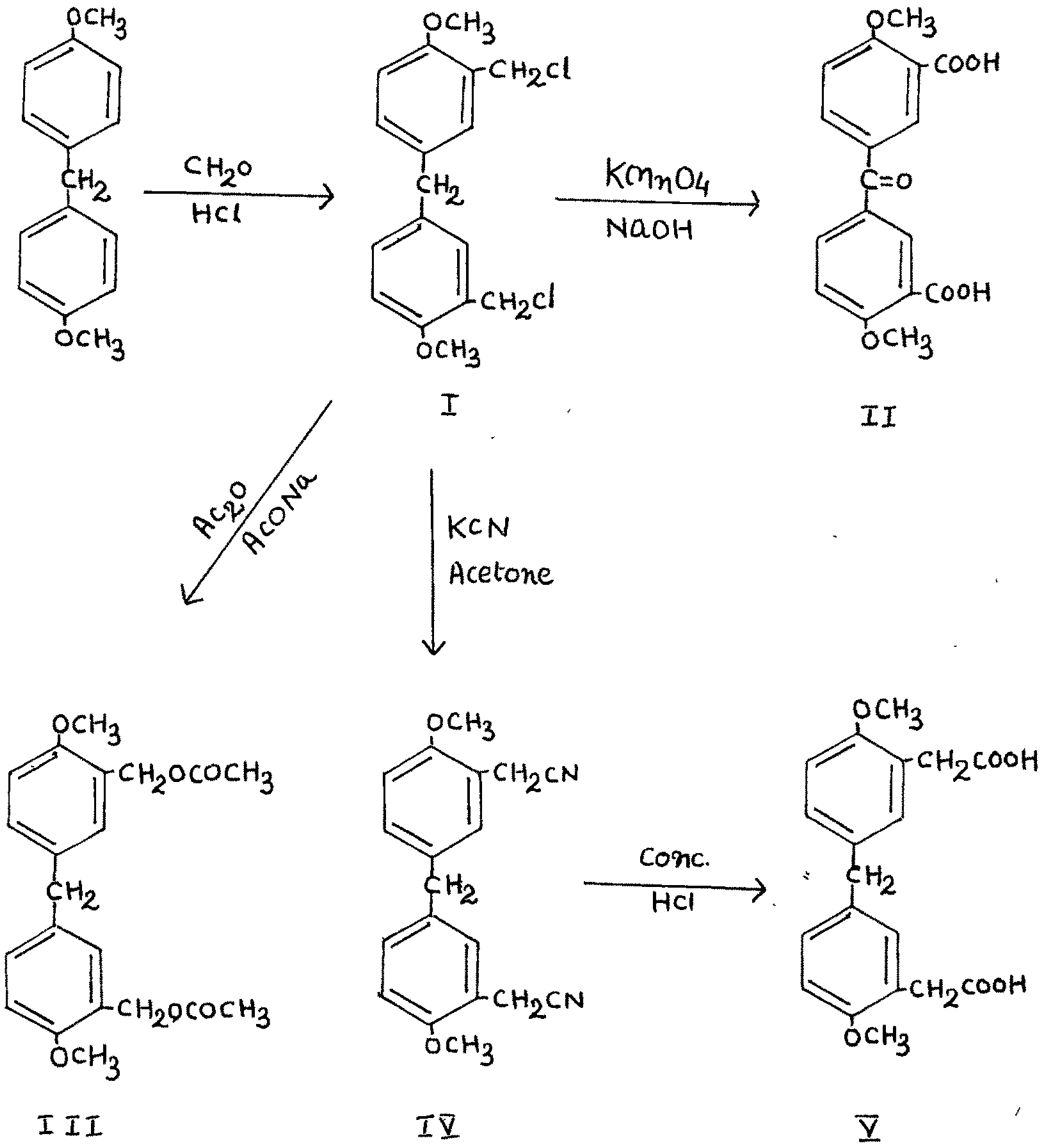
2,2'-Dihydroxydiphenyl methane on chloromethylation with two or more moles of formaldehyde gave a polymeric product even at low temperatures, from which on pure product could be isolated.

2,2'-Dimethoxydiphenyl methane on chloromethylation with paraformaldehyde and acetic acid at room temperature gave a di(chloromethyl) derivative (X) which on alkaline potassium permanganate oxidation gave a dicarboxylic acid (XI), m.p. 332°, identical with the known 2,2'-dimethoxybenzophenone-5,5'-dicarboxylic acid prepared by Balani and Sethna[24]. They reported the m.p. 328-29°. 2,2'-Dimethoxy-5,5'-di(chloromethyl)diphenyl methane structure was, therefore, assigned to the di(chloromethyl) derivative. Because of very low yield other derivatives could not be prepared.

Attempted chloromethylation of 4,4'-dihydroxydiphenyl sulfone and its dimethyl ether :

4,4'-Dihydroxydiphenyl sulfone with paraformaldehyde in acetic acid at room temperature, with or without catalyst gave the original product. Zinc chloride, aluminium chloride, a mixture of zinc chloride and aluminium chloride, stannic chloride, sulfuric acid and phosphoric acid at 80-100° gave a polymeric product. A polymeric product was also obtained when dry hydrochloric acid gas was passed in the presence of the above catalysts at room temperature for a longer period.

Similar attempts to chloromethylate 4,4'-dimethoxydiphenyl sulfone with two or more moles of formaldehyde in glacial acetic acid at 80-90° in the presence of various catalysts such as zinc chloride, aluminium chloride, a mixture of zinc chloride and aluminium chloride, stannic chloride, etc., did not succeed. In all cases the original product was obtained back.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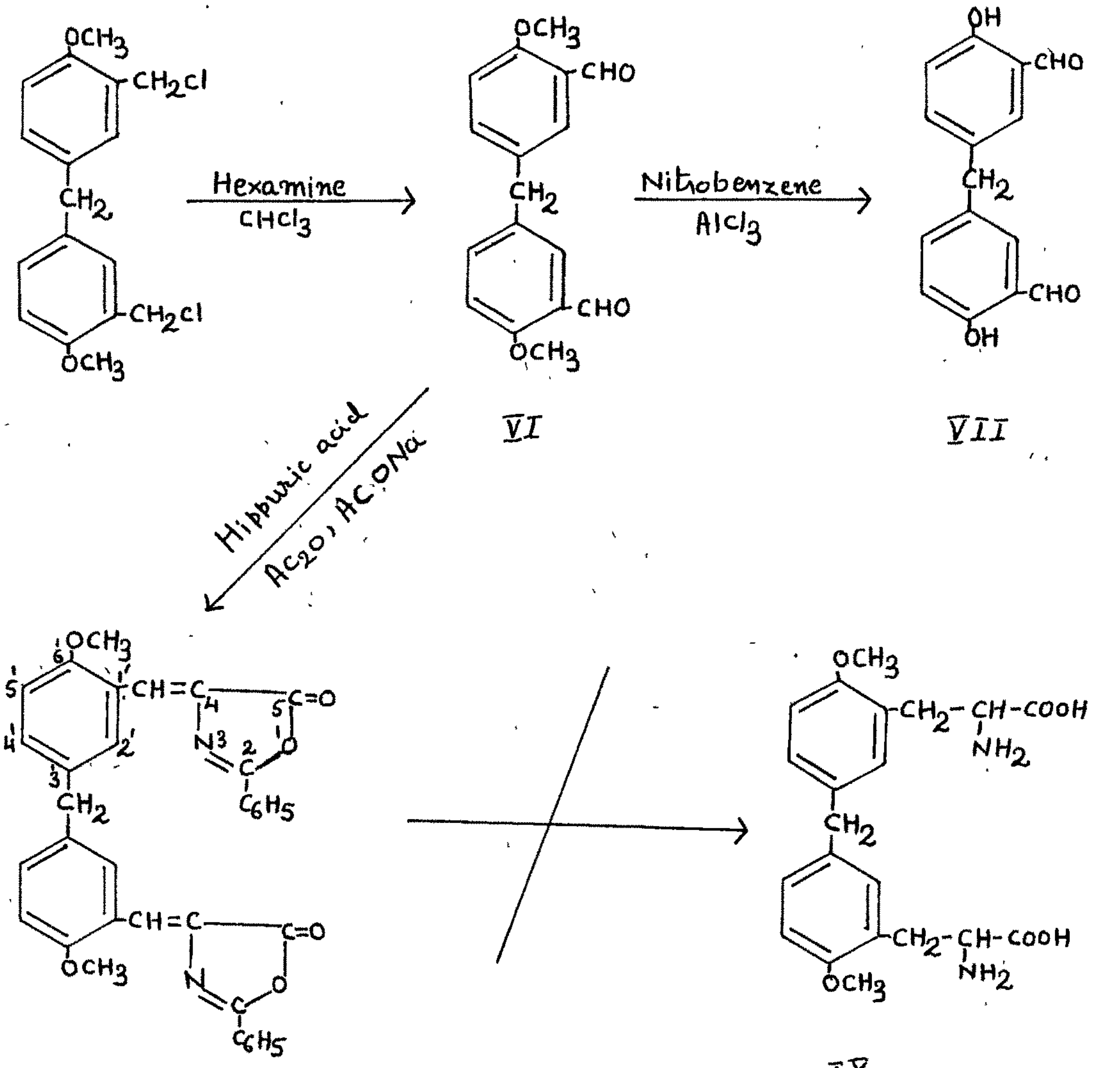

VI

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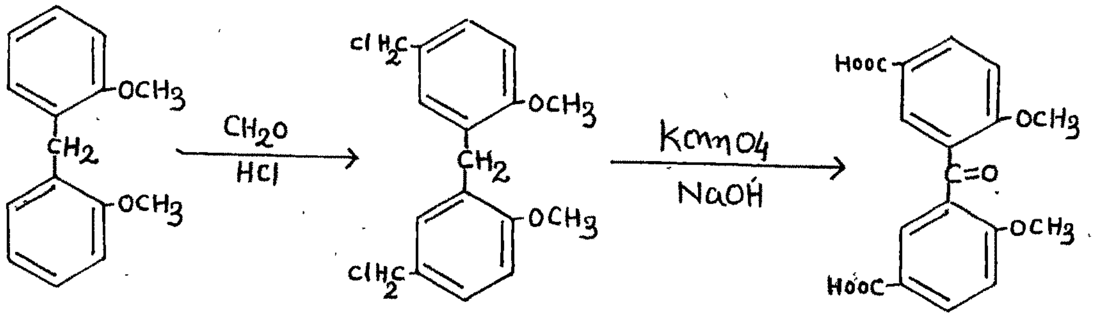

X

XI

EXPERIMENTAL

Chloromethylation of 4,4'-dimethoxydiphenyl methane : 3,3'-Di(chloromethyl)-4,4'-dimethoxydiphenyl methane :

On passing hydrochloric acid gas through a clear solution of 4,4'-dimethoxydiphenyl methane (2 g.) and paraformaldehyde (2 g.) in acetic acid (20 ml., 90 %) for 3 hr. the di(chloromethyl) derivative separated. It was filtered, washed with water, dried and crystallised from benzene-petroleum ether mixture in white shining cubes (0.8 g.), m.p. 114-15°.

Analysis : Found C, 62.55; H, 5.20; Cl, 21.88 %.

$C_{17}H_{18}Cl_2O_2$ requires : C, 62.76; H, 5.54; Cl, 21.85 %.

Oxidation : A mixture of the above di(chloromethyl) derivative (0.5 g.), potassium permanganate (2 g.) and sodium hydroxide solution (20 ml; 10 %) was refluxed for 6 hr. Excess of potassium permanganate (2 g. in all) was added in small quantities at regular intervales. The reaction mixture was filtered and the filtrate was decolourised by adding sodium sulfite solution. The clear alkaline solution was acidified with hydrochloric acid. The separated product was purified by extraction with sodium bicarbonate and crystallised from alcohol in white needles (0.2 g.), m.p. 245°. Ishiwata and Takada[29] who prepared the same compound by the oxidation of 3,3'-diformyl-4,4'-dimethoxydiphenyl methane reported m.p. 242-43°. Mixed m.p. with the same acid prepared by Balani and Sethna[25] by the oxidation of 3,3'-diacetyl-4,4'-dimethoxybenzophenone was not depressed.

3,3'-Di(acetoxymethyl)-4,4'-dimethoxydiphenyl methane :

The di(chloromethyl) derivative (0.5 g.) was refluxed with fused sodium acetate (2 g.) and acetic anhydride (5 ml.) for 1 hr. The product obtained on diluting the reaction mixture with water crystallised from benzene-petroleum ether mixture in white buds (0.3 g.), m.p. 72-73°.

Analysis : Found : C, 68.10; H, 6.28 %.

$C_{21}H_{24}O_6$ requires : C, 67.74; H, 6.45: %.

3,3'-Di(cyanomethyl)-4,4'-dimethoxydiphenyl methane :

The di(chloromethyl) derivative (1 g.) was refluxed with potassium cyanide (1 g.) and sodium iodide (0.2 g.) in dry acetone for 15 hr. The product obtained on removal of acetone was washed with water and crystallised from benzene-petroleum ether mixture in white needles (0.8 g.), m.p. 122-23°.

Analysis : Found : C, 74.59; H, 5.77; N, 9.10 %

$C_{19}H_{18}N_2O_2$ requires : C, 74.50; H, 5.88; N, 9.15 %.

3,3'-Di(carboxymethyl)-4,4'-dimethoxydiphenyl methane :

The above di(cyanomethyl) derivative (0.5 g.) was refluxed with conc. hydrochloride acid (20 ml.) for 6 hr. The separated acid was purified by bicarbonate extraction and crystallised from dil. alcohol in pale yellow needles (0.2 g.), m.p. 173°.

Analysis : Found : C, 66.01; H, 5.64 %.

$C_{19}H_{20}O_6$ requires : C, 66.26; H, 5.81 %.

3,3'-Diformyl-4,4'-dimethoxydiphenyl methane :

A mixture of 3,3'-di(chloromethyl)-4,4'-dimethoxydiphenyl methane (1 g.), hexamine (3 g.) and chloroform (20 ml.) was refluxed on a steam bath for 5 hr. The separated complex was refluxed with acetic acid (20 ml.; 50 %) for 3 hr. The product obtained on dilution of the reaction mixture with water crystallised from dilute acetic acid in white buds (0.5 g.), m.p. 135°.

Analysis : Found : C, 71.78 ; H, 5.43 %.

$C_{17}H_{26}O_4$ requires : C, 71.83 ; H, 5.63 %.

The di(2,4-dinitrophenylhydrazone) :

It was prepared as usual and crystallised from nitrobenzene in orange needles, m.p. 282°.

Analysis : Found : N, 17.07 %.

$C_{29}H_{24}N_8O_{10}$ requires : N, 17.39 %.

Demethylation : 3,3'-Diformyl-4,4'-dihydroxydiphenyl methane :

3,3'-Diformyl-4,4'-dimethoxydiphenyl methane (1 g.) was dissolved in nitrobenzene (5 ml.) and anhydrous aluminium chloride (2 g.) was added to it. The whole reaction mixture was heated in an oil bath at 110° for 1 hr. The reaction mixture was treated with ice-cold hydrochloric acid and the nitrobenzene removed by steam distillation. The residue was extracted with sodium hydroxide solution. The product obtained on acidification of the extract crystallised from dilute acetic acid in pale yellow shining needles (0.5 g.), m.p. 143°. Marvel and Tarkoy[30] reported the same m.p. It gave a violet colouration with alcoholic ferric chloride solution.

3,3'-methylene bis [2-phenyl-4(6'-methoxy)benzal-5-oxazolone] .

A mixture of 3,3'-diformyl-4,4'-dimethoxydiphenyl methane (1 g.), hippuric acid (2 g.), fused sodium acetate (2 g.) and acetic anhydride (10 ml.) was heated on a steam bath for half an hour. The reaction mixture solidified to a yellow mass. To the above reaction mixture alcohol (50 ml.) was added. The bright yellow product which separated was filtered and crystallised from nitrobenzene in yellow needles (0.6 g.), m.p. 275-76° (decomp.).

Analysis : Found : C, 73.77; H, 4.79; N, 5.17 %.
$C_{35}H_{26}N_2O_6$ requires : C, 73.67; H, 4.56; N, 4.91 %.

The above azlactone (0.5 g.) was refluxed with acetic anhydride (5 ml.) and hydriodic acid (3 ml.) in presence of red phosphorus (1 g.) for 4 hr. The reaction mixture was filtered and the filtrate was poured in ice-cold water and neutralised by dil. ammonium hydroxide solution. It was decolourised by adding sodium sulfite solution. No precipitate was obtained, therefore the solution was concentrated and cooled. White needles separated which were found on direct comparison to be of benzoic acid and the desired aminoacid (IX) could not be obtained.

Chloromethylation of 2,2'-dimethoxydiphenyl methane : 2,2'-Dimethoxy-5,5'-di(chloromethyl)diphenyl methane :

Through a mixture of 2,2'-dimethoxydiphenyl methane (1 g.) and paraformaldehyde (0.5 g.) in glacial acetic acid (10 ml.)

dry hydrogen chloride gas was passed at room temperature for 2 hr. The separated product crystallised from petroleum ether. M.p. 92-94°. Yield 0.2 g.

Analysis : Found : C, 62.79; H, 5.81; Cl, 21.66 %.

$C_{17}H_{18}Cl_2O_2$ requires : C, 62.76; H, 5.54; Cl, 21.85 %.

<u>Oxidation</u> : 2,2'-Dimethoxybenzophenone-5,5'-dicarboxylic acid :

A mixture of the above di(chloromethyl) derivative (0.5 g.), potassium permanganate (2 g.) and sodium hydroxide solution (20 ml.; 10 %) was refluxed for 6 hr. Excess of potassium permanganate (1 g.) was added in small quantities at regular intervals. The reaction mixture was filtered and the filtrate was decolourised by adding sodium sulfite solution. The clear alkaline solution was acidified with hydrochloric acid. The separated product was purified by extraction with sodium bicarbonate solution and crystallised from acetic acid, m.p. 332°. Mixed m.p. with an authentic sample, prepared according to Balani and Sethna[24], was not depressed.

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