CHAPTER IV

MANNICH REACTION ON SOME BIPHENOLS

CHAPTER IV

Mannich reaction on some phenolic compounds :- The Mannich reaction consists in the condensation of a compound containing at least one hydrogen atom of pronounced activity with an aldehyde, usually formaldehyde, and ammonia or a primary or a secondary amine.

$$B : H + CH_2O + NHRR' \dashrightarrow BCH_2NRR' + H_2O$$

The essential feature of the reaction is the replacement of the active hydrogen atom by an aminomethyl or substituted aminomethyl group. Phenols, ketones, aldehydes, acids, esters, acetylenes, nitrocompounds and heterocyclic ring systems containing either oxygen, nitrogen or sulphur are found to undergo this reaction.

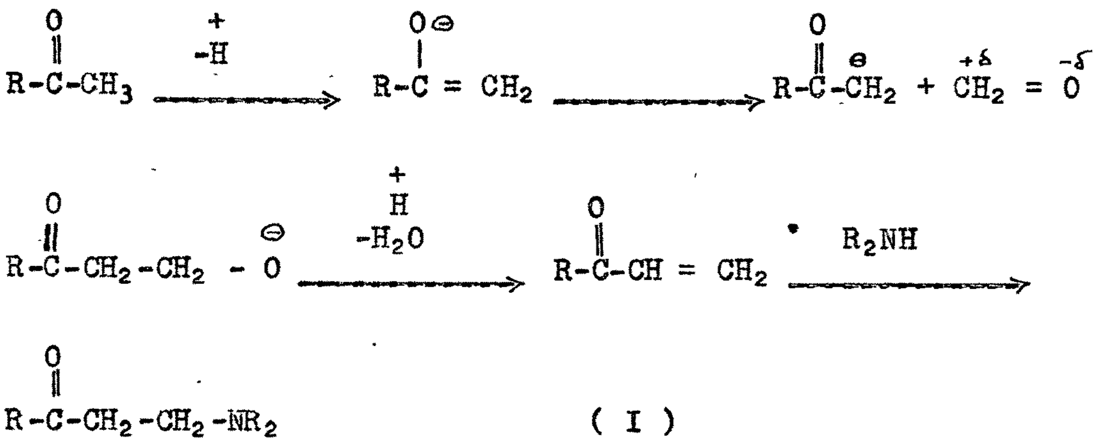
A survey of the Mannich reaction upto 1941 has been made by Blicke[1].

Mechanism :- The mechanism of the Mannich reaction has not been definitely established. Several workers have however tried to establish the mechanism. Dalglish[2] suggested a mechanism which involves formation of an α-β-unsaturated ketone (I) that adds to ammonia.

---

[1] F.F.Blicke., Organic reactions Vol. I, John Wiley and Sons., New York., 1942, p. 303.

[2] Dalgliesh., J.Am.Chem.Soc., 71, 1697 (1949).



$$R-\overset{\overset{O}{\|}}{C}-CH_3 \xrightarrow{\overset{+}{-H}} R-\overset{\overset{O^{\ominus}}{|}}{C}=CH_2 \longrightarrow R-\overset{\overset{O}{\|}}{C}-\overset{\ominus}{C}H_2 + \overset{+\delta}{C}H_2 = \overset{-\delta}{O}$$

$$R-\overset{\overset{O}{\|}}{C}-CH_2-CH_2-\overset{\ominus}{O} \xrightarrow[-H_2O]{\overset{+}{H}} R-\overset{\overset{O}{\|}}{C}-CH=CH_2 \xrightarrow{R_2NH} R-\overset{\overset{O}{\|}}{C}-CH_2-CH_2-NR_2$$

(I)

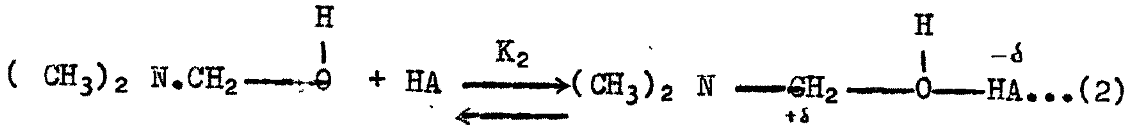
Quite a different mechanism was proposed by Alexander[3] et al. for the reaction of compounds containing active methylene group. They made a kinetic study of the reaction of ethyl malonic acid with formaldehyde and dimethylamine and based on their results they proposed a reaction mechanism in which the reaction is considered to be initialed by the reversible addition of dimethylamine and formaldehyde to give dimethylaminomethanol (I). In the presence of an acid HA, reactive hydrogen bounded addition complex formation (II) is postulated. A properly oriented collision of the complex (II) with ethyl malonic acid, probably in the transitory enol form (III) would produced water, the conjugate base A and a protonated molecule of dimethyl amino methyl malonic acid (IV). Reaction of the protonated molecule with the conjugate base A would give the free amino acid (V).

---

3. Alexander et al., J.Am.Chem.Soc., 71, 4014 (1949).

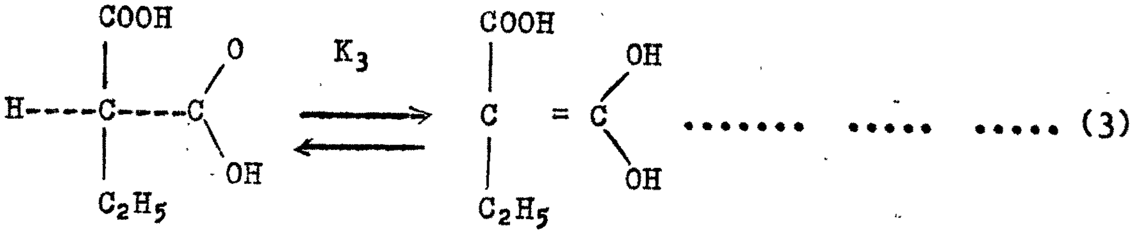
$$CH_2O + (CH_3)_2\ NH \overset{K_1}{\rightleftharpoons} (CH_3)_2\ N.CH_2OH \ ....(I)$$

(I)

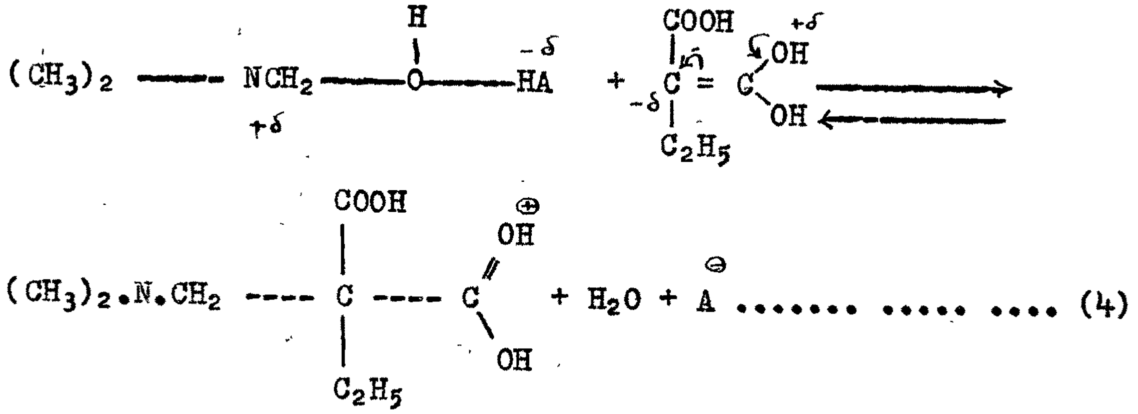


$$(CH_3)_2\ N.CH_2-\overset{H}{O} + HA \overset{K_2}{\rightleftharpoons} (CH_3)_2\ N-\underset{+\delta}{C}H_2-\overset{H}{O}-\overset{-\delta}{HA}...(2)$$

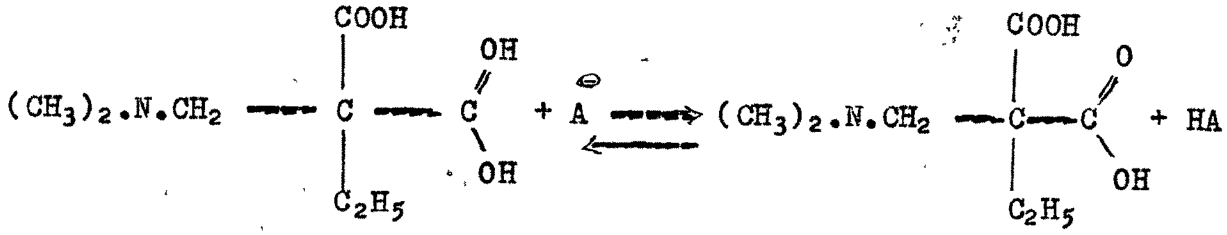
(II)



(III)



(IV)



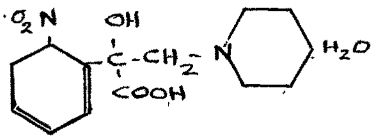
(IV)

(V)

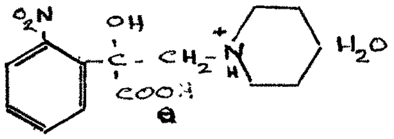
The postulation of enolization step (3) in the above mechanism was questioned by Grillot[4] et al. They found that in Mannich reactions involving optically active o-nitro mandelic acids the products formed were also optically active. Thus they argued that lack of racemization rendered inadmissible the enolization step postulated above. However, this objection has been cleared by the work of Meinwald[5] et al. who showed that products obtained by Grillot et al[4]. were not the true Mannich bases (I). They considered the products as salts and out of the two possible general structures II and III they conclusively gave the structure (II) to the products on the results of infra red absorption spectra and molecular weight determinations carried out on product from D-o-nitro mandelic acid, formaldehyde and piperidine.

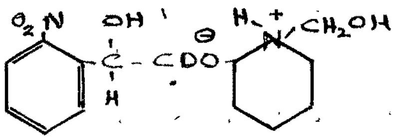
---

4. Grillot., J.Am.Chem.Soc., 72, 2813 (1950) ; 73, 5598 (1951).
5. Meinwald., Ibid., 75, 485 (1953).



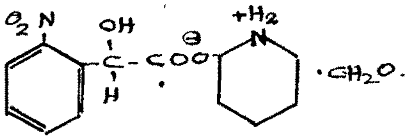
or





II

or



III

Liebermann[6] and Wagner believe that the Mannich reaction involves a dual catalysis in an amphoteric system in which the cation $R_2N\text{-}\overset{+}{C}\text{-}$ is formed from the condensation products of amine and carbonyl compound and combines finally with the anion of the reactive hydrogen compound. Formation of cation is induced by added acid or by the acidity of the reactive hydrogen compound or both. Formation of the anion is promoted by the base present or by added alkali or both. The inference that excessive acid would interfere with the primary condensation of amine and carbonyl compound and would depress the ionization tendency of the reactive hydrogen compound and that excessive alkali would decrease or prevent the formation of cation $R_2\text{-}N\text{-}C\text{-}$ and therefore would obstruct and stop the reaction were supported experimentally. Also the probability that the

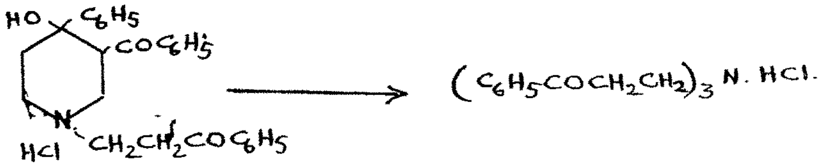
---

[6] Liebermann and Wagner., J.Org.Chem., 14, 1011 (1949).

cation originates in the alkalidene-bis-amine formed from aldehyde and amine strengthened by demonstration that methylene bis-amines, used instead of aldehydes and amines, produced normal yields.

The scope of Mannich reaction :- A large number of different types of compounds have been subjected to this reaction. Only a few illustrative reactions are given here.

Reactions with ketones :- A primary amine is the first product formed from a Mannich reaction in which ammonia or ammonium salt and formaldehyde react with a ketone. With simple ketones subsequent action of the primary amine so formed usually leads to the production of secondary amines, salts of which have been isolated and found to be stable, but the free bases change to the tertiary amines. In some instances cyclic products are obtained from ketone, formaldehyde and ammonia. For example, Mannich and Abdullah[8] obtained a substituted piperidine from acetophenone,



formaldehyde and ammonium chloride.

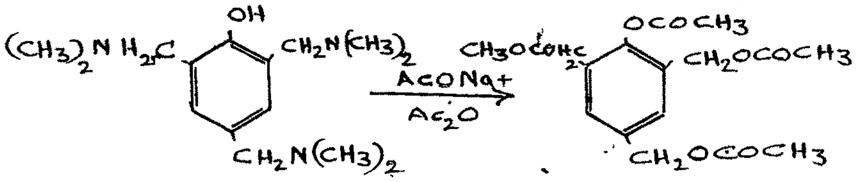
With aldehydes :- The α-hydrogen atom of the aldehyde is replaced by a substituted amino-methyl group. A secondary reaction which sometimes occurs involves the simultaneous introduction of a methylolgroup on the α-carbon atom.

---

[8] Mannich and Abdullah., Ber., 68, 113 (1935).

With acids and esters :-A number of acids and esters containing highly reactive hydrogen atoms in the α-position undergo Mannich reaction. When an acid is employed the free amine base,rather than its salt is used. Decarboxylation of the acid sometimes takes place. In the Mannich reaction of acids with primary amines the first product often undergoes further condensation to form a tertiary amine.

With phenols :- Decombe[9] conclusively proved that in the condensation of a phenol with formaldehyde and secondary amines the resulting dialkyl aminomethyl group enters the ortho or para position or both and that in no case it attaches to oxygen of the hydroxyl group. Brusson[10] and co-workers showed that when phenolic Mannich bases were treated with acetic anhydride their dimethyl aminomethyl groups were replaced by acetoxy methyl groups.



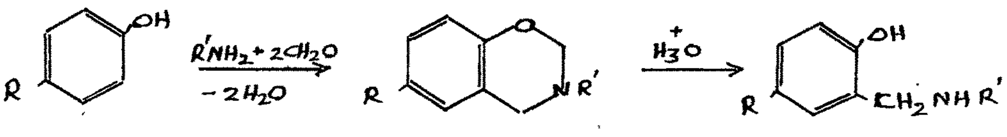
Although the reaction of phenols with formaldehyde and secondary amines have been extensively studied,analogous studies involving primary amines appear to have been limited

---

[9] Decombe., Compt.rend., 196, 866 (1933).

[10] Brusson et al., J.Am.Chem.Soc., 63, 270 (1941).

to the use of 2-aminoethanol[11] before the related work of Burke and coworkers. Reaction of equimolecular quantities of this amine with formaldehyde and certain ortho and para substituted phenols resulted in crystalline compounds having ortho or para β-hydroxy ethyl aminomethyl groups. Burke[12] showed that whereas the condensation of equimolecular quantities of para substituted phenols with formaldehyde and primary amines gave o-alkylaminomethyl-p-substituted phenols when the reaction was carried out using phenol, formaldehyde and primary amine in a molar ratio of 1:2:1 respectively the formation of substituted benzoxazine (I) a new series of compounds took place. These benzoxazines could be prepared



I II

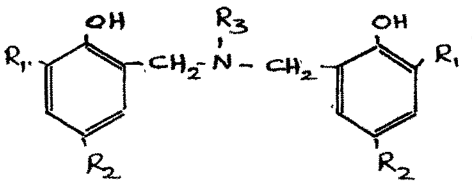
alternately from o-alkylamino-p-substituted phenols by refluxing them with excess of formaldehyde in alcoholic solution in presence of basic catalyst such as sodium hydroxide. The benzoxazine derivatives on heating with hydrochloric acid in alcoholic solution decompose readily to give formaldehyde and the corresponding o-alkyl aminomethyl-p- substituted phenols. The same authors also showed that a third kind of product N,N-bis-(2-hydroxybenzyl)-alkylamines (III) could be directly obtained in the reaction of

---

[11] Brusson., J.Am.Chem.Soc., 58, 1741 (1936).

[12] Burke., J.Am.Chem.Soc., 71, 609 (1949).

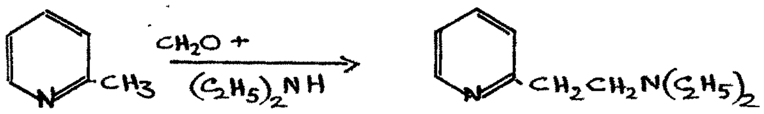
certain ortho para substituted phenols with formaldehyde and primary amines[13]. When polyhydroxy phenols were



III

condensed with formaldehyde and primary amines poly 1,3-benzoxazines were formed[14]. β-Naphthol and α-naphthol with formaldehyde and primary amines in a molar ratio of 1:2:1 respectively gave the corresponding naphthoxazino derivatives[14].

<u>Reaction with heterocyclic compounds</u> :- A number of heterocyclic systems containing nitrogen,oxygen or sulphur have been studied. In the systems containing nitrogen atom such as α-picoline and quinaldines the hydrogen of the α-methyl group is sufficiently reactive to take part in the Mannich reaction. Thus Tseou[15] and co-workers found that the condensation of α-picoline with formaldehyde and diethylamine gave 2-(β-diethyl aminomethyl) pyridine.



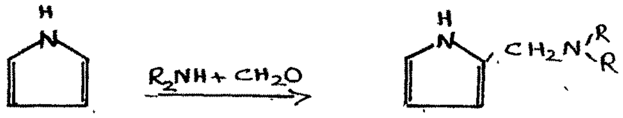
---

[13] Burke., J.Am.Chem.Soc., 74, 602 (1952).

[14] Burke and Weatherbee., J.Am.Chem.Soc., 72, 4691 (1950) ; 74, 3601 (1952).

[15] Tseou., Compt.rend., 192, 1242 (1931).

Mannich reaction with several pyrrole derivatives has been studied by Burke and co-workers[16]. Hydrogen on α-carbon atom was substituted but the resulting Mannich bases being unstable, they were characterised by their picrates.



Nixon and co-workers[17] subjected 2-methylfuran to Mannich reaction using formaldehyde and primary and secondary amines. In all cases the expected furfuryl amines or their hydrochlorides were obtained. Several chromones[18] and flavones[19] have been subjected to Mannich reaction and the expected Mannich bases were obtained. These derivatives are found to be active as powerful central nervous system stimulants especially on the brain stem, and have a cardiokinetic and hypertensive action.

Hydroxy coumarins have been subjected to Mannich reaction with primary as well as secondary amino derivatives[20;20a] and the corresponding oxazino or alkyl amino methyl derivatives have been isolated.

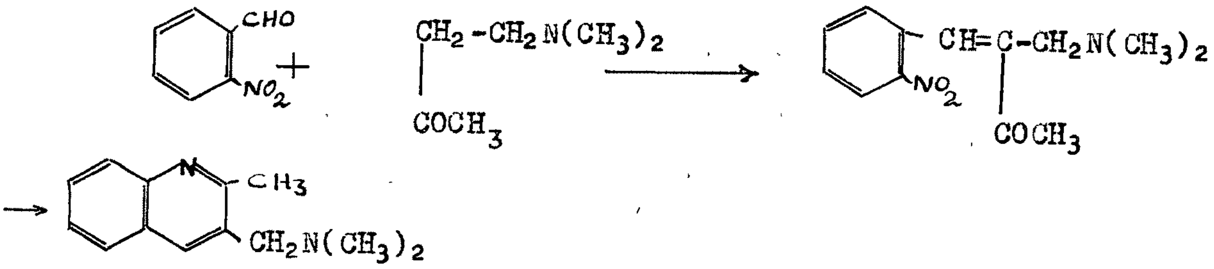
---

16. Burke and co-workers., J.Am.Chem.Soc., 76, 1294 (1954).
17. Nixon et al., Ibid., 68, 1198 (1946).
18. Wiley., Ibid., 73, 4205 (1951) ; 74, 4326 (1952).
19. P.Da Re et al., Nature 184, 362 (1959) ; J.Org.Chem., 25, 1097 (1960).
20. Desai., J.Org.Chem., 26, 5251 (1961).
20a. Patel and Sethna., J.Ind.Chem.Soc., 39, 595 (1962).

In recent years the 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, methoxymethyl, hydroxymethyl etc. and some of the Mannich bases or their reduction products are found to be important medicinal agents.

The most important characteristic property of many of the products obtained in the Mannich reaction, especially those derived from secondary amines, is the decomposition into the amine and unsaturated compound when subjected to heat or steam distillation. However, when the active hydrogen atom taking part in the Mannich reaction is on tertiary carbon atom, then the product cannot decompose to ethylenic substance.

Mannich[21] et al. found that β-dimethyl aminomethyl ketone and o-nitrobenzaldehyde reacted to give a product which upon reduction lost water to form a substituted quinoline.



---

21. Mannich et al., Arch.Pharm., 271, 116 (1933).

Many γ-substituted alcohols, obtained from the Mannich bases, have been widely used as local anaesthetics.

Caldwell and Thompson[22] have developed a new method of nuclear methylation of phenols by reducing the Mannich bases. Using this method Callin et al.[23] achieved a partial synthesis of 2,6-xylenol. Piperidines are obtained as condensation products from one mole of a primary amine two moles of formaldehyde and two moles of a ketone. Synder[18] observed that when Mannich base in acetic acid solution was treated with hexamethylene tetramine the intermediate qua~~y~~ternary salt decomposed to an aldehyde.

$$R\text{-}CH_2N(CH_3)_2 + (CH_2)_6N_4 + CH_3COOH \longrightarrow$$

$$(CH_3)_2NH + RCH_2 - N(CH_2)_6\overset{+}{N}_3 + CH_3COO^-$$

$$RCH_2N(CH_2)_6\overset{+}{N}_3 \longrightarrow RCHO$$

The intermediate quaternary salts were of the type encountered in the Sommelet reaction[24]. The conversion of primary and secondary amines to aldehydes by modified Sommelet reaction was described by Graymore et al.[25]

A number of phenolic compounds have been subjected to Mannich reaction with various primary as well as secondary amines, former comparatively less work has been done on polyhydric phenols and biphenols. This may be due to the extreme reactivity of the polyhydroxy compounds

---

[22] Caldwell and Thompson., J.Am.Chem.Soc., 61, 765 (1939).

[23] Callin et al., Ibid., 72, 2763 (1950)

[24] Sommelet Compt.rend., 157, 852 (1913).

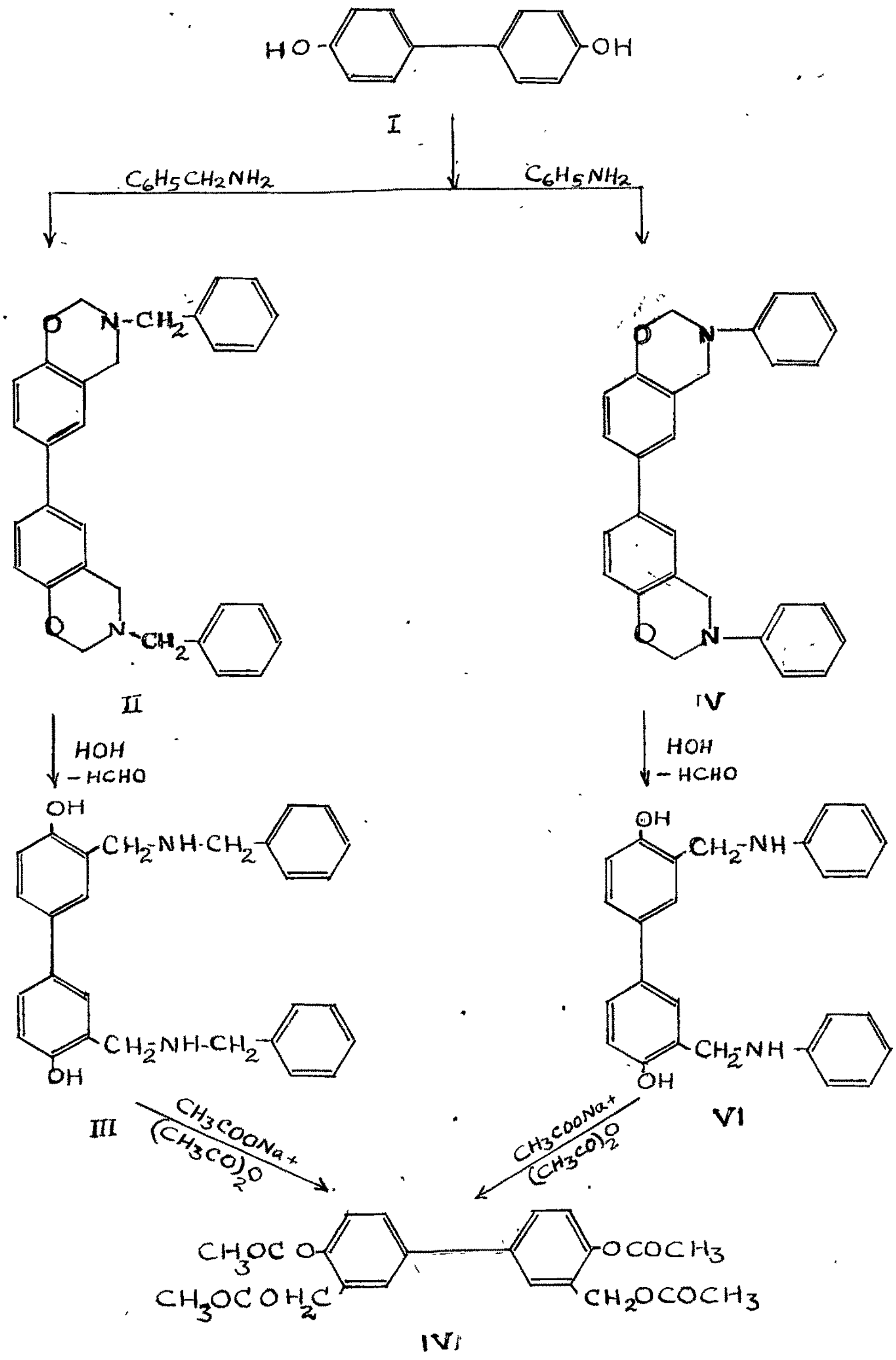
[25] Graymore et al., J.Chem.Soc., 1945, 293.

giving rise to unworkable products. But it is a general fact that the reactivity of the hydroxy group can be brought down by negative substitutents in the phenyl nucleus. Work of Burke and co-workers[17] in isolating the oxazino derivatives as the Mannich reaction products from phenol was a novelty of Mannich reaction. The present work deals with the study of the Mannich reaction with some ~~polyhydroxy phenols and~~ biphenols with various amines scuh as benzyl amine, aniline, dimethylamine, piperidine and morpholine.

Mannich reaction on 4,4'-dihydroxy biphenyl :-

(a) With benzylamine : 4,4'-Dihydroxy biphenyl (I) when treated with excess of paraformaldehyde and 2 moles of benzylamine in alcohol at room temperature gave a product which was found to be insoluble in sodium hydroxide and very sparingly soluble in hydrochloric acid. It analysed for two oxazino groups. On refluxing with alcoholic hydrochloric acid it gave formaldehyde which was identified by the preparation of its 2,4-dinitrophenyl hydrazone and another product, highly soluble in sodium hydroxide and hydrochloric acid, indicating that the sodium hydroxide insoluble compound was a bioxazinyl derivative. 3,3'-Dibenzyl-2,4,2',4'-tetrahydro-6,6'-bi-(1,3,1',3'-benzo-oxazinyl) (II) structure has therefore been assigned to the bioxazinyl derivative. The hydrolysed product, therefore, should be 4,4'-dihydroxy-3,3'-di-benzylaminomethyl biphenyl (III). On treatment with fused sodium acetate and acetic anhydride 4,4'-dihydroxy-3,3'-di-benzylaminomethyl biphenyl afforded 4,4'-diacetoxy-3,3'-di-acetoxymethyl biphenyl (IV). Brusson et al[10] obtained the same type of acetoxymethyl derivative when dimethyl aminomethyl derivative was treated with sodium acetate and acetic anhydride. With one mole of benzyl amine and excess of paraformaldehyde only the bibenzoxazinyl derivative (II) was formed.

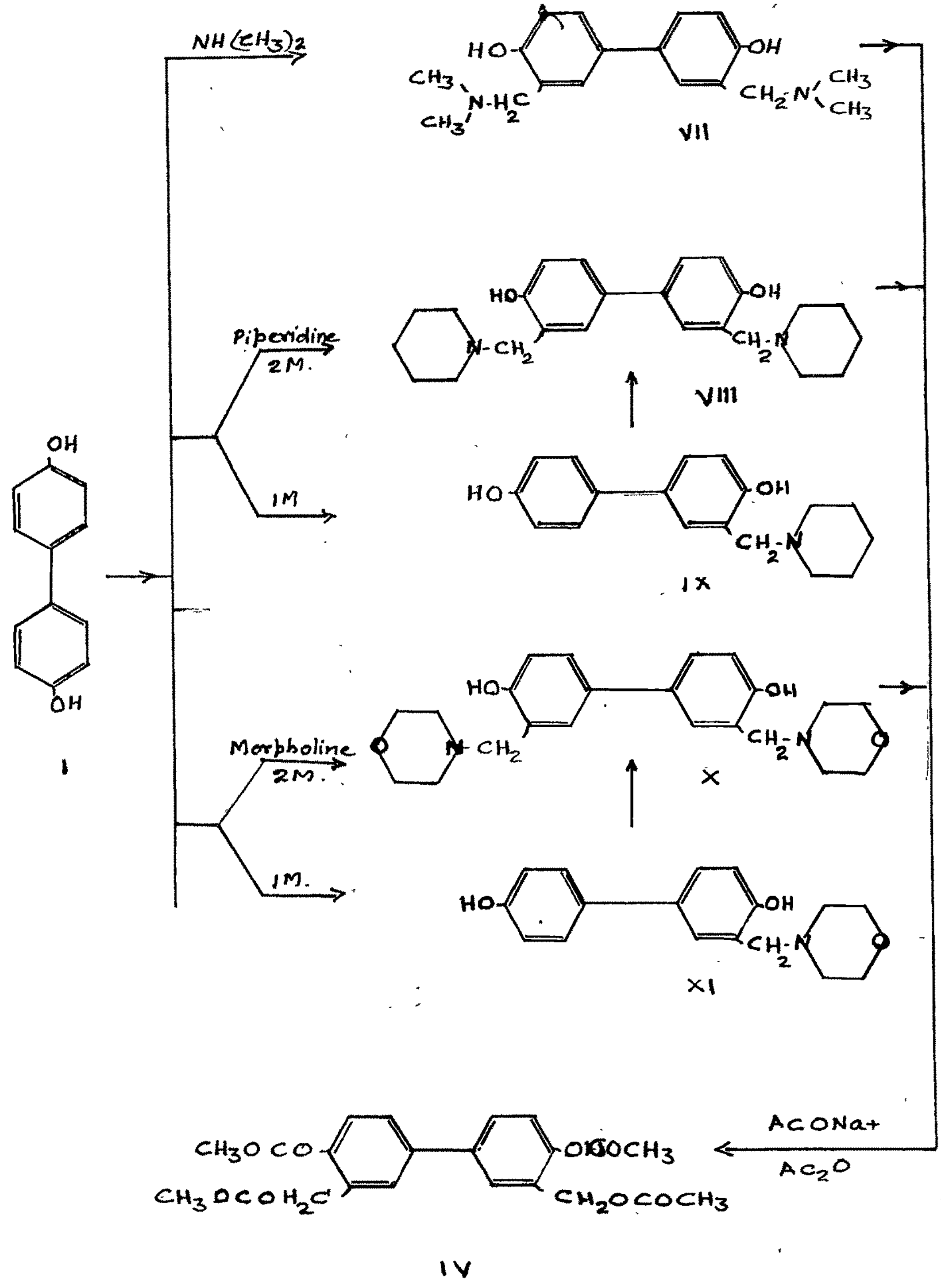
(b) With aniline : When 4,4'-dihydroxy biphenyl (I) was subjected to Mannich reaction with excess of aniline and paraformaldehyde in alcohol at room temperature a product


HO
OH
I
C6H5CH2NH2
C6H5NH2
O
N-CH2
O
N-CH2
II
O
N
O
N
V
HOH
- HCHO
HOH
- HCHO
OH
CH2-NH-CH2
CH2-NH-CH2
OH
III
OH
CH2-NH
CH2-NH
OH
VI
CH3COONa+
(CH3CO)2O
CH3COONa+
(CH3CO)2O
CH3OC O
CH3OC O H2C
OCOCH3
CH2OCOCH3
IV

was obtained which was found to be a bi-oxazinyl derivative on the basis of its insoluble character in sodium hydroxide and hydrochloric acid and its analysis for two benzoxazino groups. 3,3'-Diphenyl-2,4,2',4'-tetrahydro-6,6'-bi-(1,3,1',3'-benzoxazinyl) structure (V) has therefore been assigned to the product. On hydrolysis with alcoholic hydrochloric acid the bibenzoxazinyl derivative afforded the 4,4'-dihydroxy-3,3'-dianilinomethyl biphenyl (VI) and formaldehyde. 4,4'-Dihydroxy-3,3'-dianilinomethyl biphenyl on treatment with acetic anhydride and sodium acetate gave 4,4'-diacetoxy-3,3'-diacetoxymethyl biphenyl (IV) described earlier.

With dimethylamine : 4,4'-Dihydroxy-3,3'-di-(dimethyl aminomethyl) biphenyl (VII) was the product obtained when 4,4'-dihydroxybiphenyl (I) was treated with excess of dimethylamine and paraformaldehyde since it gave the known 4,4'-diacetoxy-3,3'-diacetoxymethyl biphenyl (IV) on treatment with acetic anhydride and sodium acetate.

With piperidine : With one mole of piperidine and paraformaldehyde in alcohol 4,4'-dihydroxy biphenyl (I) gave a product which analysed for one piperidinomethyl group. On further Mannich reaction with excess of piperidine it gave a product to which 4,4'-dihydroxy-3,3'-dipiperidinomethyl biphenyl (VIII) structure has been assigned on the basis of the formation of the known 4,4'-diacetoxy-3,3'-diacetoxymethyl biphenyl (IV) with acetic anhydride and sodium acetate. 4,4'-Dihydroxy-3-piperidinomethyl biphenyl (IX) structure has therefore been assigned to the mohopiperidinomethyl derivative.


NH(CH3)2
HO
OH
CH3
N-H2C
CH3
CH2-N
CH3
CH3
VII
Piperidine
2M.
HO
OH
N-CH2
CH2-N
VIII
1M
HO
OH
CH2-N
IX
OH
OH
I
Morpholine
2M.
HO
OH
N-CH2
CH2-N
X
1M.
HO
OH
CH2-N
XI
AcONa+
Ac2O
CH3OCO
OCOCH3
CH3OCOH2C
CH2OCOCH3
IV

(e) With morpholine : 4,4'-Dihydroxy-3-morpholinomethyl biphenyl (XI) structure has been assigned to the product obtained when 4,4'-dihydroxy biphenyl (I) was subjected to Mannich reaction with one mole of morpholine and excess of paraformaldehyde in alcohol at room temperature because on further Mannich reaction with excess of morpholine it gave 4,4'-dihydroxy-3,3'-dimorpholinomethyl biphenyl (X) which gave the known 4,4'-diacetoxy-3,3'-diacetoxymethyl biphenyl (IV) with sodium acetate and acetic anhydride. The same 4,4'-dihydroxy-3,3'-dimorpholinomethyl biphenyl (X) was also obtained when 4,4'-dihydroxy biphenyl (I) was subjected to Mannich reaction with excess of morpholine and paraformaldehyde in alcohol.

4,4'-Dimethoxy biphenyl did not undergo Mannich reaction with any of the primary or secondary amines and paraformaldehyde.

Attempted Mannich reaction on 2,2'-dihydroxy biphenyl : 2,2'-Dihydroxy biphenyl on Mannich reaction with the above primary as well as secondary amines and paraformaldehyde in alcohol gave a pasty productsfrom which no pure product could be isolated. Its dimethyl ether also did not undergo Mannich reaction with any of the primary or secondary amines and paraformaldehyde in alcohol.

EXPERIMENTAL

Mannich reaction on 4.4'-dihydroxybiphenyl :

6.6'-Bis-(3-dibenzyl-2.4-dihydro-1.3-benzoxazinyl) :- To a mixture of paraformaldehyde (1.5 g. ; 0.05 moles) and benzylamine (3.2 g. ; 0.03 moles) in alcohol (20 c.c.) finely powdered 4,4'-dihydroxybiphenyl (1.85 g. ; 0.01 mole) in alcohol (20 c.c.) was added and the reaction mixture kept overnight at room temperature. The solvent was allowed to evaporate and the pasty product was dissolved in benzene and filtered. The solid obtained on removal of the solvent from the filtrate crystallised from benzene-petroleum ether in white needles, m.p.142°. Yield 1.5 g. The product was slightly soluble in hydrochloric acid, but insoluble in sodium hydroxide.

Analysis : 4.896 mg. of the substance gave 14.402 mg. of carbon dioxide and 2.648 mg. of water. 8.292 mg. of the same substance gave 0.463 c.c. of nitrogen at 29° and 748 mm. pressure.

Found : C = 80.3 % ; H = 6.1 % ; N = 6.2 %.

$C_{30}H_{28}N_2O_2$ requires : C = 80.4 % ; H = 6.3 % ; N = 6.3 %.

4,4'-Dihydroxy-3,3'-di-(benzylaminomethyl) biphenyl:- The above bi-benzoxazinyl derivative (1 g.) was refluxed with alcoholic hydrochloric acid (10:5) on a wire gauze in a distilling flask and the distillate was collected in water (25 c.c.). More alcoholic acid (20 c.c. ; 1:1 by volume) was added and the distillation was continued till a solid began to separate out in the distilling flask. It was dissolved by the addition of more ethanol and the solution was neutralised with just sufficient sodium carbonate solution. The white solid obtained crystallised from benzene, m.p. 112°.

Analysis : 4.764 mg. of the substance gave 13.782 mg. of carbon dioxide and 2.900 mg. of water. 9.286 mg. of the same substance gave 0.533 c.c. of nitrogen at 33° and 750 mm. pressure.

	Found	: C = 79.0 % ; H = 6.8 % ; N = 6.3 %.
$C_{28}H_{28}N_2O_2$	requires	: C = 79.2 % ; H = 6.6 % ; N = 6.6 %.

Treatment of a portion of the distillate with 2,4-dinitrophenyl hydrazine gave a yellow crystalline product which crystallised from ethanol in bright yellow needles, m.p. 166°. Mixed m.p. with an authentic specimen of the 2,4-dinitrophenyl hydrazone of formaldehyde was not depressed.

4,4'-Diacetoxy-3,3'-di-(acetoxymethyl) biphenyl :- 4,4'-Dihydroxy-3,3'-di-(benzylaminomethyl) biphenyl (0.5 g.) was heated with acetic anhydride (5 c.c.) and fused sodium acetate (1 g.) for 2 hours on a steam bath. The solid obtained on adding the reaction mixture to water crystallised from acetic acid in needles, m.p. 145°

Analysis : 4.396 mg. of the substance gave 10.310 mg. of carbon dioxide and 2.172 mg. of water.

	Found	: C = 64.0 % ; H = 5.5 %.
$C_{22}H_{22}O_8$	requires	: C = 63.8 % ; H = 5.3 %.

6,6'-Bi-(3-phenyl-2,4-dihydro-1,3-benzoxazinyl) :- Paraformaldehyde (0.9 g. ; 0.03 mole) was dissolved in absolute alcohol (5 c.c.) containing potassium hydroxide (0.01 g.) by gentle warming. Aniline (2.2 ml. ; 0.025 mole) and absolute alcohol (5 c.c.) were then added to the reaction mixture. 4,4'-dihydroxybiphenyl(1.85 g. ; 0.01 mole) in alcohol (15 c.c.) was added and the reaction mixture was kept overnight. The alcohol was evaporated off and the paste obtained was triturated with petroleum ether (b.p. 40-60°) and then extracted with benzene. The residue obtained after the removal of benzene on repeated crystallisations from benzene-petroleum ether mixture gave needles, m.p. 205°.

It was insoluble in sodium hydroxide and slightly soluble in hydrochloric acid.

Analysis : 4.462 mg. of the substance gave 13.010 mg. of carbon dioxide and 2.274 mg. of water. 8.910 mg. of the same substance gave 0.524 c.c. of nitrogen at 33° and 750 mm. pressure.

Found : C = 79.6 % ; H = 5.7 % ; N = 6.5 %.

$C_{28}H_{24}N_2O_2$ requires : C = 80.0 % ; H = 5.7 % ; N = 6.7 %.

Along with the oxazino derivative some white crystalline product which was highly soluble in petroleum ether (b.p. 40-60°) was also isolated which was found to be identical with the Schiff's bases obtained when aniline was condensed with paraformaldehyde in alcohol, m.p. 140°.

Analysis : 7.990 mg. of the substance gave 0.95 c.c. of nitrogen at 33°C and 750 mm. pressure.

Found : N = 13.1 %.

C_7H_7N requires : N = 13.3 %.

4,4'-Dihydroxy-3,3'-di-(anilinomethyl) biphenyl :- To the above bi-benzoxazinyl derivative (1 g.), alcoholic hydrochloric acid 15 c.c.(2:1) was added and the reaction mixture distilled on a wire gauze, the distillate was collected in water. During the course of the distillation dilute alcohol (20 c.c. ; 1:1 by volume) was added and the distillation was stopped after a solid began to separate out in the distilling flask. The solution was neutralised with just sufficient quantity of sodium bicarbonate solution, and the precipitate crystallised from benzene in white needles, m.p. 150°.

Analysis : 4.406 mg. of the substance gave 12.670 mg. of carbon dioxide and 2.556 mg. of water. 9.086 mg. of the same substance gave 0.574 c.c. of nitrogen at 31°C and 749 mm. pressure.

Found : C = 78.5 % ; H = 6.5 % ; N = 7.0 %.

$C_{26}H_{24}O_2N_2$ requires : C = 78.8 % ; H = 6.2 % ; N = 7.1 %.

When the above anilinomethyl derivative was treated with sodium acetate and acetic anhydride it afforded 4,4'-diacetoxy-3,3'-diacetoxymethyl biphenyl identical with the one described earlier.

Mannich reaction on 4,4'-dihydroxy biphenyl with dimethyl amine : 4,4'-Dihydroxy-3,3'-di-(dimethyl-)aminomethyl) biphenyl :- Paraformaldehyde (0.9 g. ; 0.03 mole) was dissolved in warm alcohol (10 c.c.) and dimethylamine (3 c.c. ; 37 % aqueous solution 0.03 mole) was added gradually with external cooling. 4,4'-Dihydroxy biphenyl (1.85 g. ; 0.01 mole) in 15 c.c. alcohol was then added and kept overnight at room temperature. The product separated out was collected and crystallised from benzene in white cubes, m.p. 165°.

It was soluble in hydrochloric acid as well as sodium hydroxide.

Analysis : 5.996 mg. of the substance gave 15.870 mg. of carbon dioxide and 4.40 mg. of water. 8.784 mg. of the same substance gave 0.752 c.c. of nitrogen at 33°C and 750 mm. pressure.

Found : C = 72.2 % ; H = 8.1 % ; N = 9.4 %.
$C_{18}H_{24}N_2O_2$ requires : C = 72.0 % ; H = 8.0 % ; N = 9.3 %.

Treatment of the above di-(dimethyl)aminomethyl) derivative with sodium acetate and acetic anhydride gave the known 4,4-diacetoxy-3,3'-diacetoxymethyl biphenyl.

4,4'-Dihydroxy-3,3'-di-piperidinomethyl biphenyl :- To a mixture of paraformaldehyde (0.9 g. ; 0.03 mole) and piperidine (2.1 g. ; 0.025 mole) in alcohol (20 c.c.) 4,4'-dihydroxy biphenyl (1.85 g. ; 0.01 mole) in 20 c.c. of alcohol was added ~~and~~ the mixture kept overnight, at room temperature. The solvent was evaporated off and the pasty product was extracted with benzene. Benzene was evaporated off and the product was crystallised from benzene-petroleum ether mixture. M.P. 158°. It was soluble in hydrochloric acid as well as sodium hydroxide.

Analysis : 4.668 mg. of the substance gave 12.988 mg. of the carbon dioxide and 3.400 mg. of water. 8.310 mg. of the same substance gave 0.554 c.c. of nitrogen at 32°C and 750 mm. pressure.

Found : C = 75.9 % ; H = 8.1 % ; N = 7.4 %.

$C_{24}H_{32}O_2N_2$ requires : C = 75.8 % ; H = 8.4 % ; N = 7.4 %.

On refluxing with sodium acetate and acetic anhydride the above di-piperidinomethyl derivative gave 4,4'-diacetoxy-3,3'-di-acetoxymethylbiphenyl described earlier.

__4,4'-Dihydroxy-3-piperidinomethyl biphenyl__ :- To a mixture of paraformaldehyde (0.3 g. ; 0.01 mole) and piperidine (0.85 g. ; 0.01 mole) in alcohol (15 c.c.) 4,4'-dihydroxybiphenyl (1.85 g. ; 0.01 mole) in 20 c.c. alcohol was added and kept overnight. The alcohol was evaporated off and the product obtained was crystallised from benzene in long needles, m.p. 218°.

Analysis : 4.284 mg. of the substance gave 11.968 mg. of carbon dioxide and 2.794 mg. of water. 8.662 mg. of the same substance gave 0.385 c.c. of nitrogen at 35°C and 753 mm. pressure.

Found : C = 76.2 % ; H = 7.3 % ; N = 4.9 %.

$C_{17}H_{19}O_3N$ requires : C = 76.3 % ; H = 7.4 % ; N = 4.9 %.

The above piperidinomethyl biphenyl derivative was again treated with excess of paraformaldehyde and piperidine in alcohol at room temperature and working up as usual gave crystals of 4,4'-dihydroxy-3,3'-di-piperidinomethyl biphenyl. M.P. and mixed m.p. with the product obtained earlier was not depressed.

<u>4,4'-Dihydroxy-3,3'-di-morpholinomethyl biphenyl</u> :- To a solution of 4,4'-dihydroxy biphenyl (1.85 g. ; 0.01 mole) in alcohol (15 c.c.) paraformaldehyde (0.9 g. ; 0.03 mole) and morpholine (2.2 g. ; 0.025 mole) in alcohol (15 c.c.) was added and kept overnight. Alcohol was evaporated off and the product obtained was crystallised from benzene in white cubes. M.P. 187°. It was soluble in sodium hydroxide and also in hydrochloric acid.

<u>Analysis</u> : 4.460 mg. of the substance gave 11.314 mg. of carbon dioxide and 2.720 mg. of water. 9.416 mg. of the same substance gave 0.633 c.c. of nitrogen at 32°C and 754 mm. pressure.

Found : C = 69.2 % ; H = 6.8 % ; N = 7.5 %.
$C_{22}H_{28}N_2O_4$ requires : C = 68.8 % ; H = 7.3 % ; N = 7.3 %.

The above di-morpholinomethyl derivative on treatment with sodium acetate and acetic anhydride afforded 4,4'-diacetoxy-3,3'-diacetoxymethyl biphenyl identical with the one obtained earlier.

<u>4,4'-Dihydroxy-3-morpholinomethyl biphenyl</u> :- To a solution of 4,4'-dihydroxy biphenyl (1.85 g. ; 0.01 mole) in alcohol (15 c.c.) a mixture of paraformaldehyde (0.3 g.; 0.01 mole) and morpholine (0.85 g. ; 0.01 mole) was added

slowly and the mixture kept overnight. The solvent was evaporated off and the product obtained was crystallised from benzene, m.p. 218°. It was soluble in hydrochloric acid and also in sodium hydroxide.

Analysis : 4.494 mg. of the substance gave 11.794 mg. of carbon dioxide and 2.818 mg. of water. 6.732 mg. of the same substance gave 0.296 c.c. of nitrogen at 34°C and 753 mm. pressure.

Found : C = 71.6 % ; H = 7.0 % ; N = 4.8 %.

$C_{17}H_{19}O_3N$ requires : C = 71.7 % ; H = 6.7 % ; N = 4.9 %.

The above morpholinomethyl derivative on further Mannich reaction with excess of paraformaldehyde and morpholine gave the 3,3'-morpholinomethyl derivative. M.P. and mixed m.p. with the product obtained earlier was not depressed.

Attempted Mannich reaction on 4,4'-dimethoxy biphenyl:- Paraformaldehyde (1.2 g. ; 0.04 moles) was dissolved in absolute alcohol (10 c.c. containing 0.1 g. of potassium hydroxide) by gentle warming. Benzylamine (3.3 c.c. ; 0.03 mole) was then added to the reaction mixture. 4,4'-Dimethoxy biphenyl (2.1 g. ; 0.01 mole) was added and the reaction mixture refluxed on a steam bath for 4 hrs. On cooling the original product separated out. The same result was seen when other amino derivatives like aniline, dimethylamine, piperidine and morpholine were used.

Attempted Mannich reaction on 2,2'-dihydroxybiphenyl:- To a mixture of paraformaldehyde (0.6 g. ; 0.02 mole) and

2,2'-dihydroxybiphenyl (1.8 g. ; 0.01 mole) in absolute alcohol (10 c.c.) benzylamine (2.2 c.c. ; 0.02 mole) was added. The reaction mixture kept overnight. On evaporation of the solvent pasty product was obtained from which no pure product could be isolated.

The experiment was repeated with dimethylamine instead of benzylamine but the same type of pasty mass was obtained from which no pure product could be isolated.

Mannich reaction on 2,2'-dimethoxy biphenyl with benzylamine and dimethylamine did not succeed.