CHAPTER III

MANNICH REACTION ON SOME HYDROXYCOUMARINS

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Mannich reaction consists in the condensation of ammonia, a primary amine or secondary amine usually as the hydrochloride, with formaldehyde and a compound containing at least one hydrogen atom of pronounced reactivity.

$$C_6H_5COCH_3 + CH_2O + R_2NH{\cdot}HCl \longrightarrow C_6H_5COCH_2CH_2NR_2{\cdot}HCl + H_2O$$

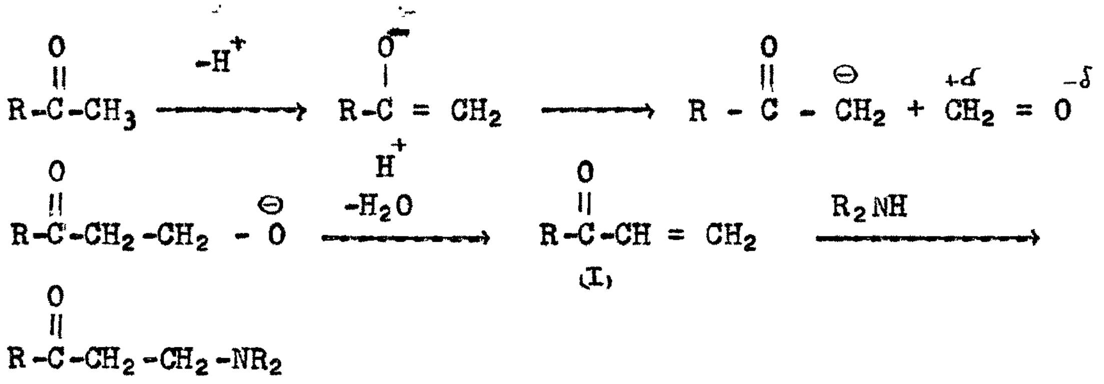
The essential feature of the reaction is the replacement of the active hydrogen atom by an aminomethyl or substituted aminomethyl group. The product from acetophenone, formaldehyde and a secondary amine salt is an example. Phenols, ketones, aldehydes,acids, esters, acetylenes, nitrocompounds and heterocyclic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

When aqueous formaldehyde is used the condensation may be carried out with or without organic solvents. Alcohol and acetic acid have been generally employed. A mixture of equivalent amounts of benzene and nitrobenzene or benzene alone are useful.

Burke and co-workers (1) have used dioxan with very good results. When paraformaldehyde is used, an organic solvent is required. Burke et al (loc.cit.) employed catalytic quantity of alcoholic potassium hydroxide to effect the depolymerisation of paraformaldehyde. The time limit required for the reaction depends upon the nature of the compound containing active hydrogen and of the amine, or amine salt and upon the boiling point of the solvent employed. Thus in the reactions of phenols with formaldehyde and primary amines the reaction is generally complete in about two hours time. It is found that the reaction may be complete within a few minutes of refluxing.

Mechanism of the Mannich Reaction :

Mechanism of reaction has not yet been definitely established. Dalgliesh (2) suggested a mechanism which involves formation of an α-B-unsaturated ketone (I) that adds ammonia.



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

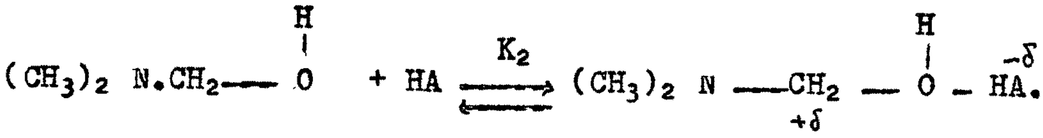
$$R-\overset{\overset{O}{\|}}{C}-CH_2-CH_2-\overset{\ominus}{O} \xrightarrow{\overset{H^+}{-H_2O}} \underset{(I)}{R-\overset{\overset{O}{\|}}{C}-CH=CH_2} \xrightarrow{R_2NH}$$

$$R-\overset{\overset{O}{\|}}{C}-CH_2-CH_2-NR_2$$

Quite a different mechanism was proposed by Alexander et al. (3) for the reaction of compounds containing active methynyl group. They made a kinetic study of the reaction of ethyl malonic acid with formaldehyde and dimethyl amine and based on their results they proposed a reaction mechanism in which the reaction is considered to be initiated by the reversible addition of dimethylamine and formaldehyde to give dimethylaminomethanol. In the presence of an acid HA, a 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 produce water, the conjugate base A and a protonated molecule of dimethylaminomethyl malonic acid (IV). Reaction of the protonated molecule with the conjugate base A would give the free amino acid (V).

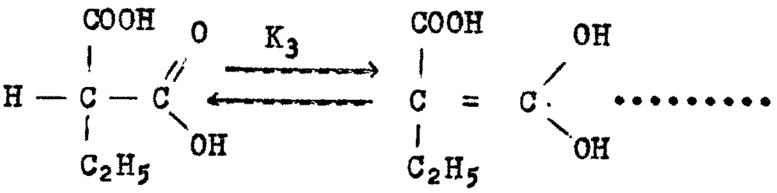
$$CH_2O + (CH_3)_2NH \xrightleftharpoons{K_1} (CH_3)_2N.CH_2OH \text{ ....(I)}$$

(I)



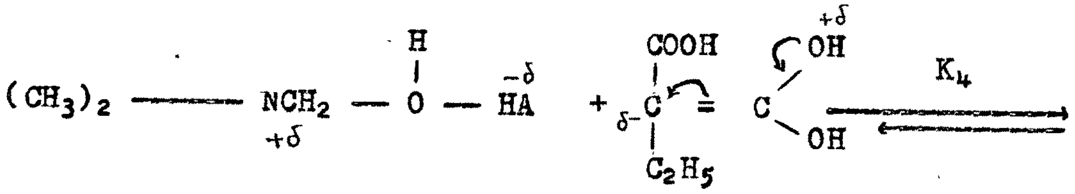
$$(CH_3)_2N.CH_2-\overset{H}{\overset{|}{O}} + HA \xrightleftharpoons{K_2} (CH_3)_2N-\underset{+\delta}{CH_2}-\overset{H}{\overset{|}{O}}-\overset{-\delta}{HA} \text{....(2)}$$

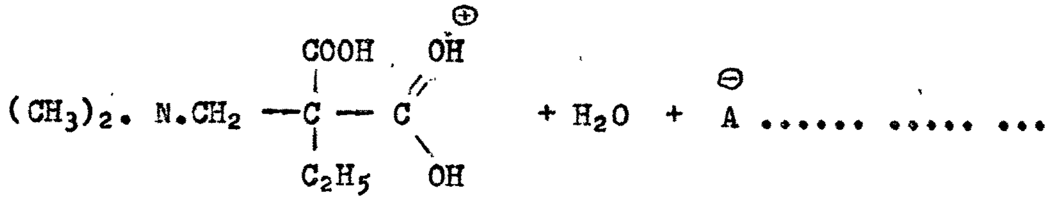
(II)



.... (3)

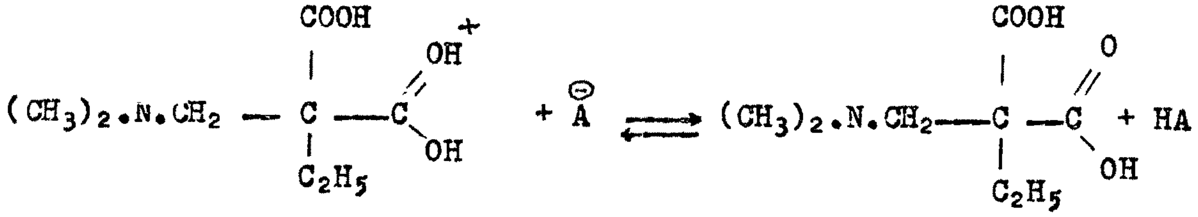
(III)





$$(CH_3)_2.\ N.CH_2-\underset{C_2H_5}{\overset{COOH}{C}}-C\begin{matrix}\overset{\oplus}{O}H\\ OH\end{matrix}\quad + H_2O + \overset{\ominus}{A}\ \ldots\ldots\ \ldots\ldots\ \ldots\ (4)$$

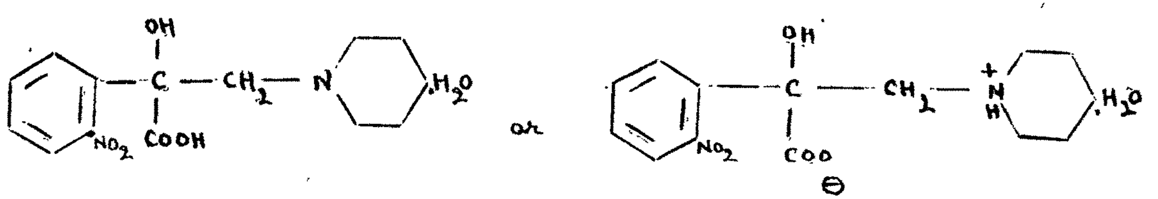
(IV)



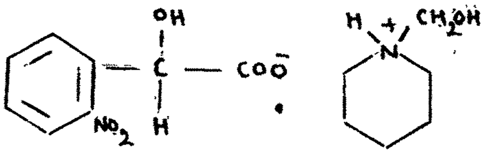
$$(CH_3)_2.N.CH_2-\underset{C_2H_5}{\overset{COOH}{C}}-C\begin{matrix}\overset{+}{O}H\\ OH\end{matrix}\ + \overset{\ominus}{A} \rightleftharpoons (CH_3)_2.N.CH_2-\underset{C_2H_5}{\overset{COOH}{C}}-C\begin{matrix}O\\ OH\end{matrix}\ + HA$$

(IV) (V)

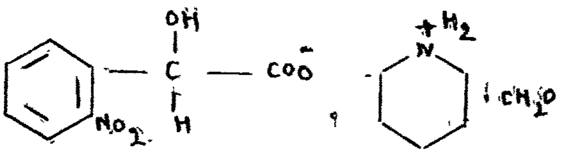
The postulation of enolisation step (3), in the above mechanism was questioned by Grillot et al. (4). They found that in Mannich reactions involving optically active o-nitro mandelic acids the products formed were also optically active. Thus they argued that lack of racemization rendered inadmissible the enolization step postulated above. However, this objection has been cleared by the excellent work of Meinwald et al. (5) who showed that products obtained by Grillot et al. (loc.cit.) 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.



I



II



III

Lieberman and Wagner (6) believe that the Mannich reaction involves a dual catalysis in an emphoteric system in which the cation $R_2 \; N - \overset{+}{C} -$ 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 inferences 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 $R_2 \; N - \overset{|+}{\underset{|}{C}} -$ and therefore would obstruct or stop the reaction were supported experimentally. Also the probability that the cation originates in the alkylidene-bis-amine formed from aldehyde and amine was strengthened by demonstration that methylene-bis-amines, used instead of aldehydes and amines, produced normal yields.

Various types of compounds having reactive hydrogen have been subjected to this reaction. Only a few illustrative reactions are mentioned 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.

$$C_6H_5COCH_3 + CH_2O + (CH_3)_2\ NH.\ HCl \xrightarrow[\text{reflux}]{\text{Alcohol}}$$

$$C_6H_5COCH_2.CH_2N(CH_3)_2.\ HCl$$

Certain ketonic amines of the type illustrated afford on reduction physiologically active amino alcohols of value in therapy.

Reaction with aldehydes :

The α-hydrogen atom of the aldehyde is substituted by a substituted amino methyl group. A secondary reaction which some times occurs involves the simultaneous introduction of a methylol group on the α-carbon atom.

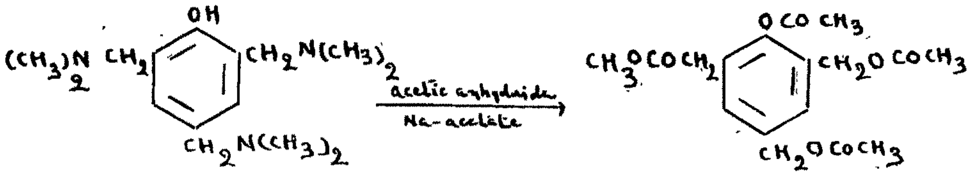
Reaction with acids and esters :

Different 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.

Reaction with phenols :

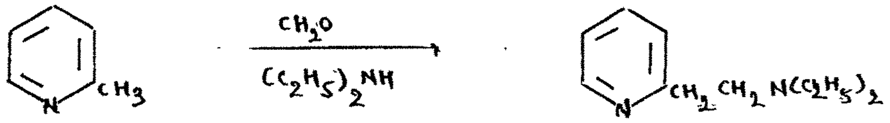
Decombe (7) has proved that in the Mannich reaction of a phenol with formaldehyde and secondary amines the resulting dialkylamino-methyl group enters the ortho or para-position or both and in no case it attaches to oxygen of the hydroxyl group.

Brusson and co-workers (8) have reported that when phenolic Mannich bases were treated with acetic anhydride their dimethylaminomethyl groups were replaced by acetoxymethyl groups.

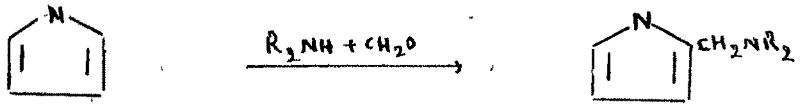


Reaction with heterocyclic compounds :

A number of heterocyclic systems containing nitrogen,oxygen or sulphur have been studied. In case of α-picolines and quinaldines the hydrogen of the α-methyl groups is sufficiently reactive to take part in the Mannich reaction. Thus, Tseou and co-workers (9) have reported the formation of 2-(B-diethylaminomethyl)pyridine when α-picoline, formaldehyde and diethylamine were condensed.



Mannich reaction with pyrrole has been studied by number of workers. Hydrogen on α-carbon atom was substituted.



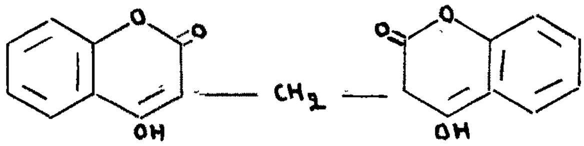
Burke and co-workers (10) have carried out the reaction on several pyrroles with formaldehyde and primary amines.

2-Methyl furan was subjected to Mannich reaction by Nixon and co-workers (11) using formaldehyde, primary and secondary amine.

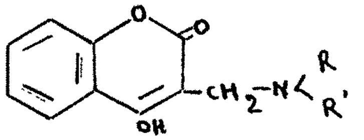
Wiley (12) carried out Mannich reaction on 6-methoxy-, 6-chloro-, 6-methyl-, and 7-methoxychromones with formaldehyde and different secondary amine hydrochlorides and obtained the corresponding 3-(dialkylaminomethyl) chromonehydrochlorides.

P.Da Re. et al. (13) reported the Mannich reaction on 7-hydroxy-2,3-dimethyl-, 2-methyl-3-ethyl-, 2-ethyl-3-methyl-chromones with dimethylamine,diethylamine, morpholine and piperidine and formalin and obtained the corresponding 8-dimethylaminomethyl chromones. Similar results were obtained in the case of 3-methyl and 3-ethyl flavones. These derivatives are reported to act as powerful central nervous system stimulants especially on the brain stem and have a cardiokinetic and hypertensive action.

Robertson and Link (14) attempted to prepare Mannich bases from 4-hydroxycoumarin, paraformaldehyde and the aminehydrochlorides but failed instead the bis product 3',3'-methylene bis-4-hydroxycoumarin, was obtained.

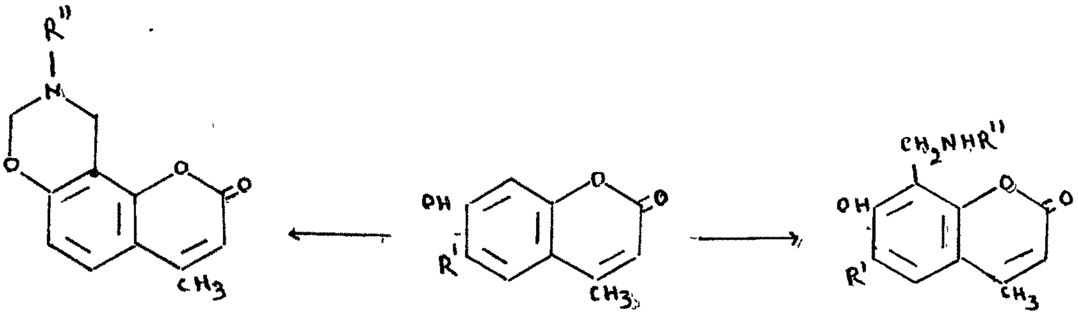


They have observed that the order in which the reactants are added is important. A series of 3-substituted aminomethyl-4-hydroxycoumarins ha~~s~~ve been synthesised by an application of the Mannich reaction.



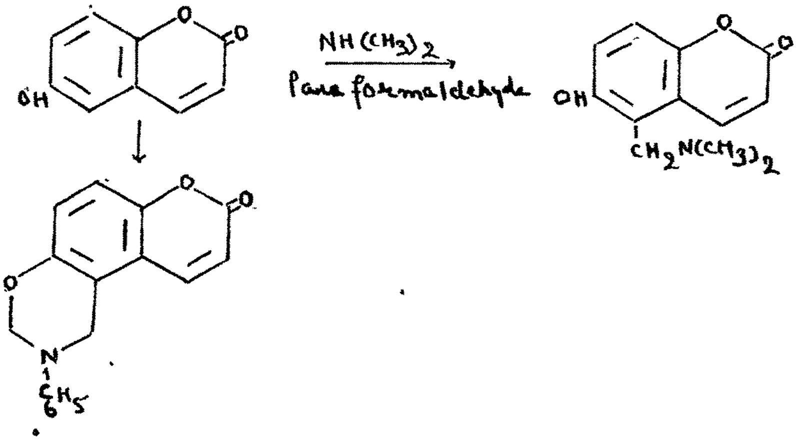
R=H or alkyl
R' = alkyl

Desai R.B. (15) studied the Mannich reaction on 5-hydroxy-, 6-hydroxy and 7-hydroxycoumarins with ~~formation~~ paraformaldehyde and primary and secondary amines.



R'=H
R''=$CH_2C_6H_5$, C_6H_5

Patel and Sethna (16) have applied Mannich reaction ~~on~~ to 7-hydroxycoumarin, 6-hydroxycoumarin, ethyl-7-hydroxycoumarin-3-carboxylate and obtained the corresponding alkylaminomethyl and oxazinoderivatives. For example, 6~~7~~-hydroxycoumarin gave with paraformaldehyde and aniline oxazinoderivative and with dimethyl amine the ~~8~~ 5-dimethyl-aminomethyl derivative.

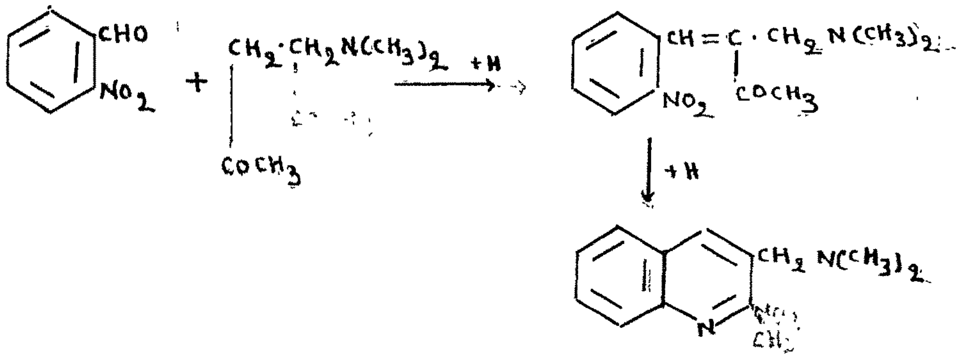


Applications of Mannich reaction :

~~Recently~~ The Mannich reaction has proved to be an important tool in the field of synthetic organic chemistry. The resulting products of the Mannich reaction may be further transformed into a variety of compounds. A few of these may be mentioned here. Some of the Mannich bases and their reduction products have proved to be important medicinal agents.

The most useful 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.

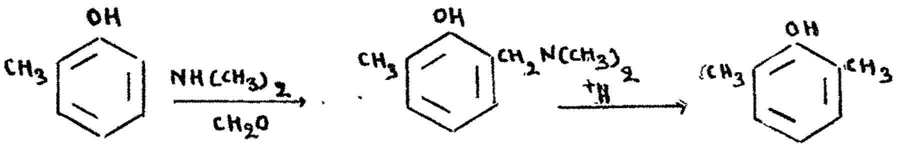
Mannich et al. (17) found that B-dimethylaminoethyl methylketone and o-nitrobenzaldehyde reacted to give a product which upon reduction lost water to form a substituted quinoline.



Synthesis of amino alcohols :

The β-substituted amino ketones or aldehydes have been reduced to the corresponding γ-substituted amino alcohols. Many such amino alcohols in the form of their esters especially benzoate and p-amino benzoates have been widely used as local anaesthetics.

Caldwell and Thompson (18) have developed a new method for nuclear methylation of phenols which consists in the hydrogenolysis of the dimethylaminomethyl derivative obtained by Mannich reaction, on ~~these~~ this basis Callin et al (19) achieved a practical synthesis of 2,6-xylenol.



~~Synder~~ Snyder (20) observed that when Mannich base in acetic acid solution was treated with hexamethylenetetraamine the intermediate quaternary salt decomposed to an aldehyde thus

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

$$(CH_3)_2NH + R\ CH_2 - \overset{+}{N}(CH_2)_6N_3 + CH_3CO\overset{-}{O}$$

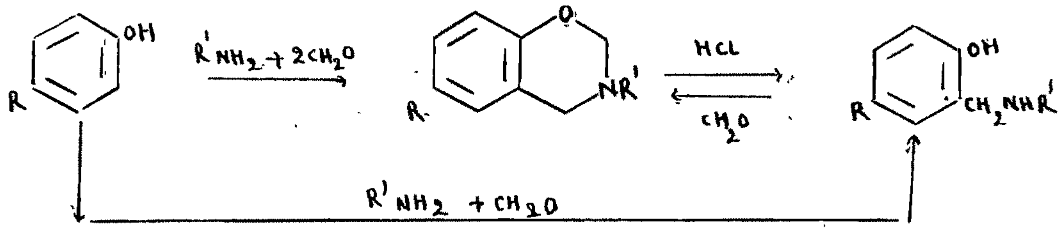
$$RCH_2\ N(CH_2)_6\ \overset{+}{N_3} \longrightarrow R\ CHO$$

The intermediate quaternary salts were of the type encountered in the Sommelet synthesis (21). The conversion of primary and secondary amines to aldehydes by modified Sommelet reaction was described by Graymore et al (22).

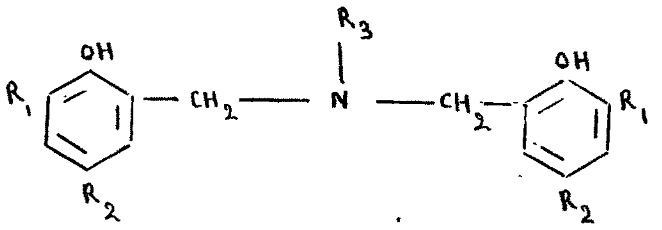
Synthesis of 1,3-oxazino derivative :

Burke (23) showed that whereas the condensation of equimolecular quantities of para substituted phenols with formaldehyde and primary amines gave o-alkylamino-methyl-p-substituted phenols, when the reaction was carried out using phenol, formaldehyde and primary amine in a molar ratio of 1:2:1 respectively ~~resulted in~~ the formation of substituted benzoxazines took place. ~~a new series of compounds formed~~.

These benzoxazines could be prepared alterna~~tiv~~tely from o-alkylamino-p-substituted phenols by refluxing them with excess of formaldehyde in alcoholic solution in the presence of a basic catalyst such as sodium hydroxide. Benzoxazine derivatives on heating with hydrochloric acid in alcoholic solution decompose readily to give formaldehyde and the corresponding o-alkylamino methyl-p-substituted phenols.



Burke and co-workers (24) showed that a third kind of product N,N-bis-(2-hydroxybenzyl) alkylamine~~s~~ could be directly obtained.



The present work deals with the application of Mannich reaction ~~on~~ to 7,8-dihydroxy-4-methylcoumarin, 5-hydroxy-4-methylcoumarin, methyl-5-hydroxy-4-methylcoumarin-6-carboxylate and 8-hydroxycoumarin. Different primary and secondary amines have been ~~were~~ used.

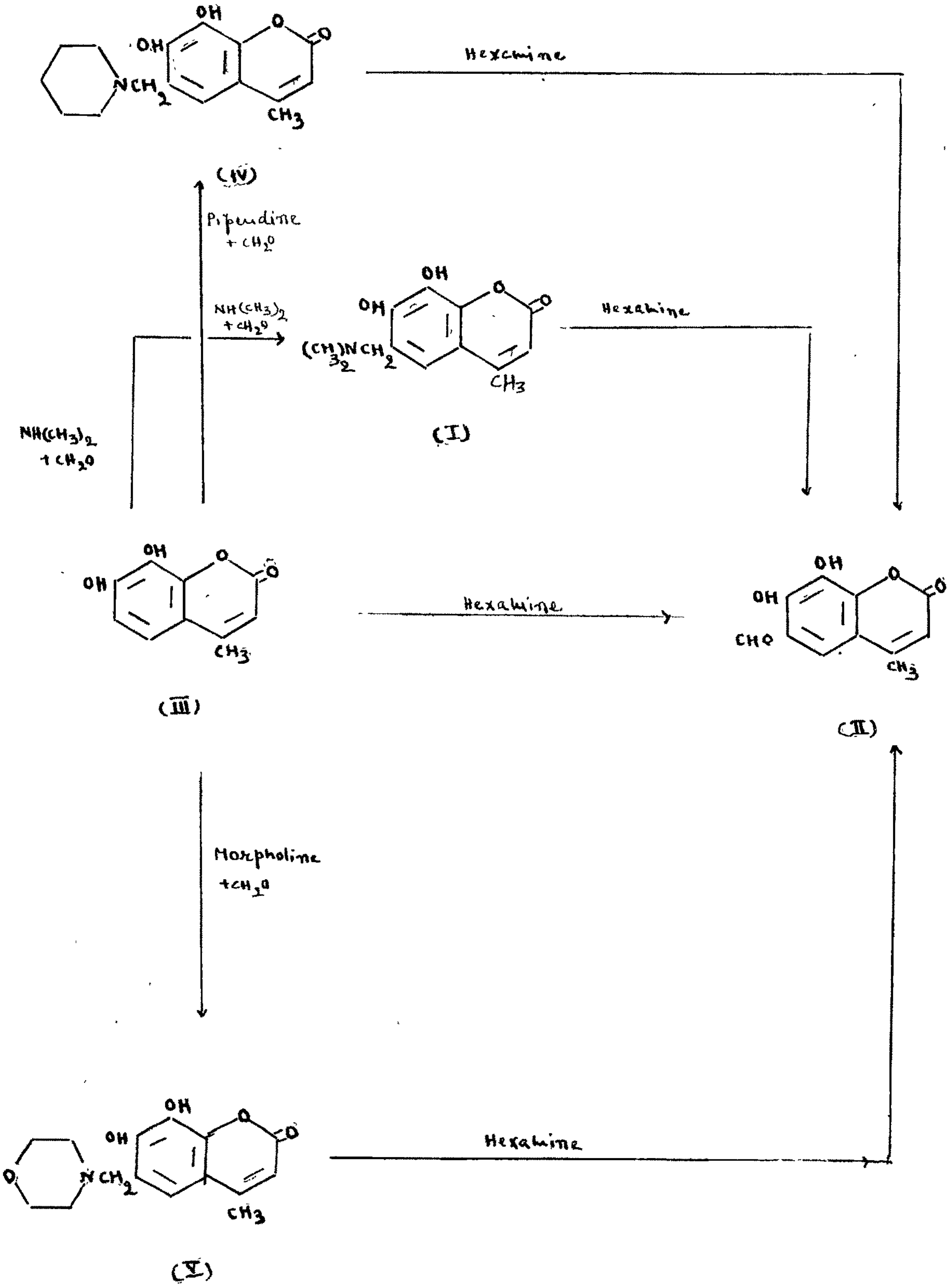
With primary amines when 2 moles of formaldehyde were used the formation of 1,3-oxazino derivative was observed in most cases whenever the reaction took place.

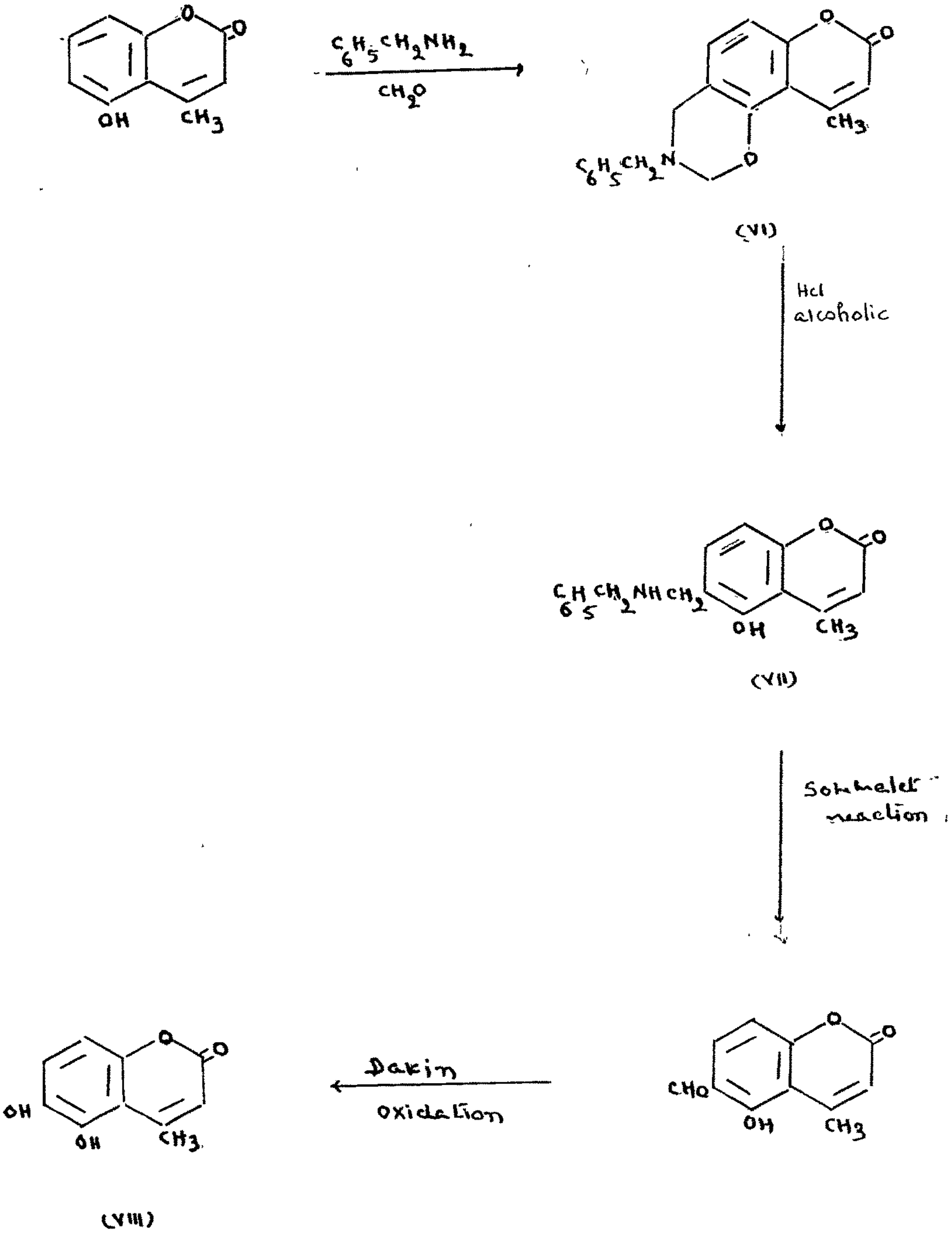
Mannich reaction on 7,8-dihydroxy-4-methylcoumarin

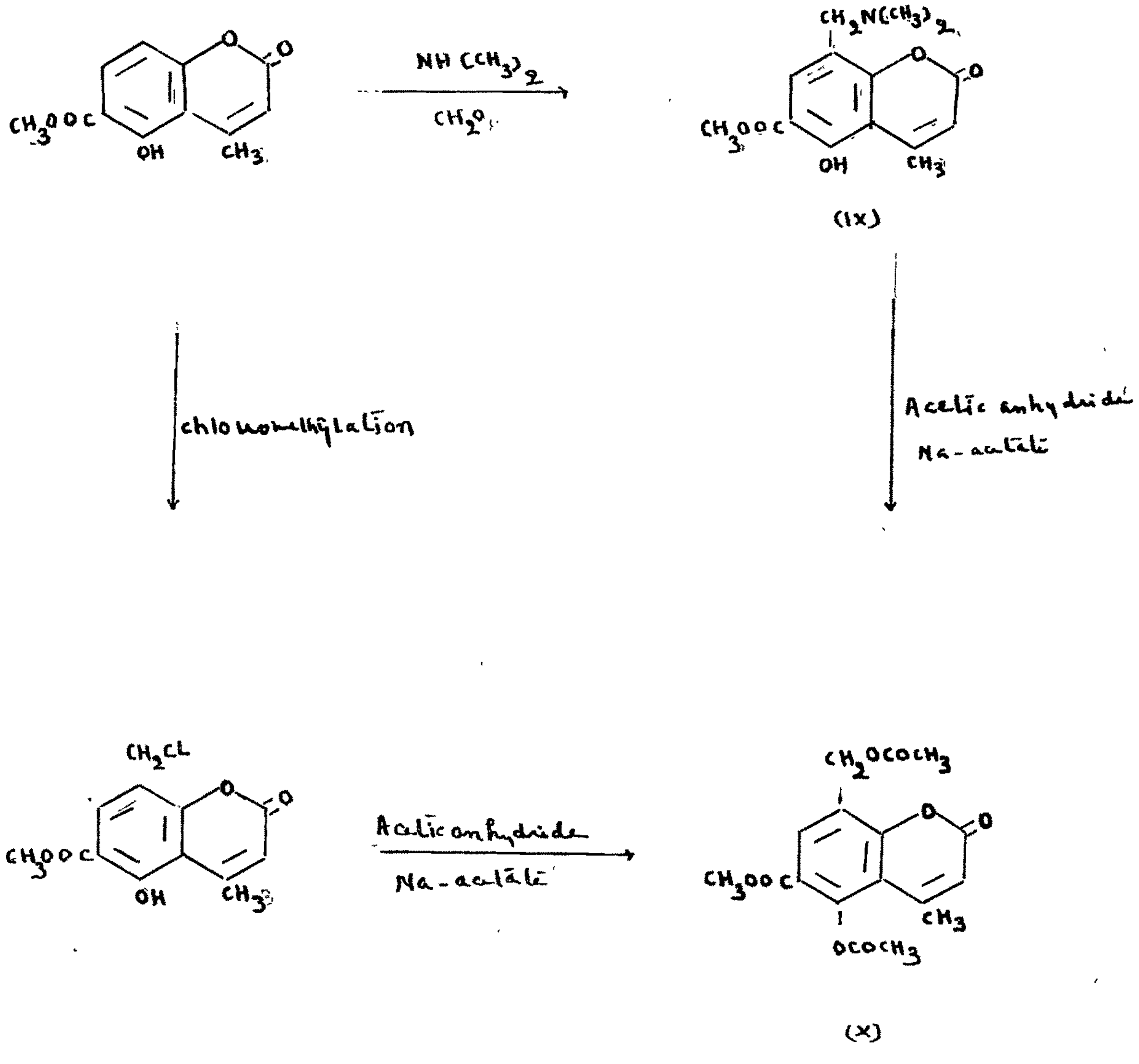
7,8-Dihydroxy-4-methylcoumarin, formalin and dimethylamine gave a compound to which 7,8-dihydroxy-6-dimethylaminomethyl-4-methylcoumarin (I) structure has been assigned because on treatment with hexamethylene tetramine it gave the known 7,8-dihydroxy-6-formyl-4-methylcoumarin (25) (II) as seen by direct comparison.

Condensation of 7,8-dihydroxy-4-methylcoumarin (III), formalin and piperidine furnished a product, which has been assigned 7,8-dihydroxy-6-piperidinomethyl-4-methylcoumarin (IV) structure as it gave the known 6-formyl derivative on Sommelet reaction.

The 6-morpholinomethylcoumarin (V) derivative resulted in the condensation of 7,8-dihydroxy-4-methylcoumarin,


OH
OH
NCH2
CH3
(IV)
Hexamine
Piperidine + CH2O
NH(CH3)2 + CH2O
OH
OH
(CH3)2NCH2
CH3
(I)
Hexamine
NH(CH3)2 + CH2O
OH
OH
CH3
(III)
Hexamine
OH
OH
CHO
CH3
(II)
Morpholine + CH2O
OH
OH
NCH2
CH3
(V)
Hexamine


$C_6H_5CH_2NH_2$
CH_2O
OH
CH_3
$C_6H_5CH_2N$
(VI)
Hcl
alcoholic
$C_6H_5CH_2NHCH_2$
(VII)
Sommelet
reaction
CHO
Dakin
oxidation
(VIII)


CH$_3$OOC
OH
CH$_3$
O
O
NH(CH$_3$)$_2$
CH$_2$O
CH$_2$N(CH$_3$)$_2$
CH$_3$OOC
OH
CH$_3$
(IX)
chloromethylation
Acetic anhydride
Na-acetate
CH$_2$Cl
CH$_3$OOC
OH
CH$_3$
Acetic anhydride
Na-acetate
CH$_2$OCOCH$_3$
CH$_3$OOC
CH$_3$
OCOCH$_3$
(X)

Mannich reaction on 8-hydroxycoumarin

8-Hydroxycoumarin has been subjected to Mannich reaction with formalin and benzylamine, piperidine and aniline.

8-Hydroxycoumarin, formalin and benzylamine in equimolecular quantities gave a compound to which 2'H-3'-benzyl-3',4'-dihydro-1',3'-oxazino-5',6'-7,8-coumarin (XI) structure has been assigned, as the product was insoluble in alkali and on treatment with alcoholic hydrochloric acid it gave formaldehyde and 8-hydroxy-7-benzylaminomethylcoumarin (XII). This was further subjected to Sommelet reaction when 8-hydroxy-7-formylcoumarin described earlier was obtained as seen by direct comparison.

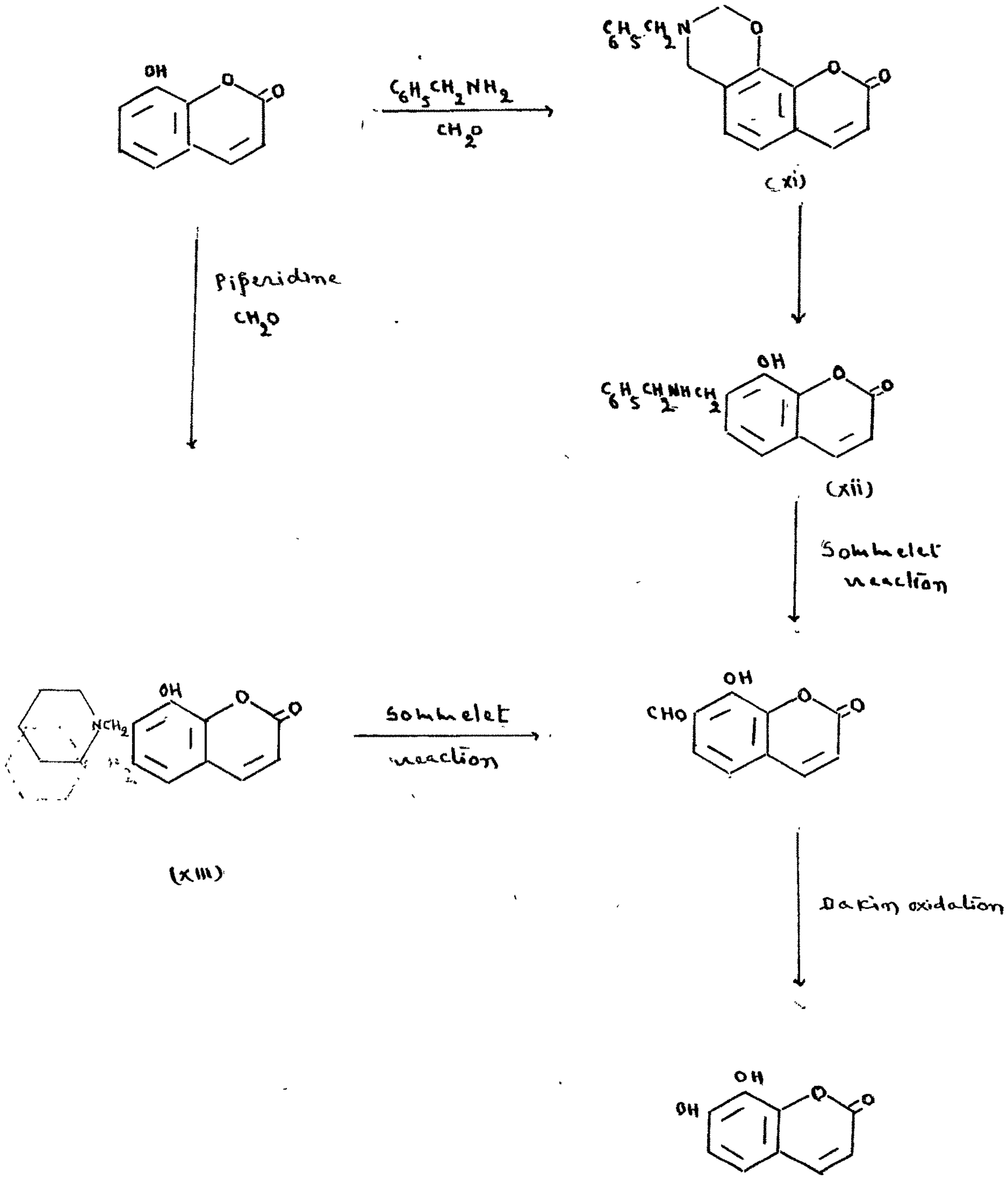
8-Hydroxycoumarin, formalin and piperidine in equimolecular quantities gave a compound to which the 8-hydroxy-7-piperidinomethylcoumarin (XIII) structure has been assigned because on treatment with hexamethylenetetramine it gave the 8-hydroxy-7-formylcoumarin described before.

* * * * *

The condensation of 7,8-dihydroxy-4-methylcoumarin, 5-hydroxy-4-methylcoumarin, methyl-5-hydroxy-4-methylcoumarin-6-carboxylate and 8-hydroxycoumarin with aniline gave complex unworkable products under different experimental conditions.

Attempted Mannich reaction on 5,7-dihydroxy-4-methylcoumarin

5,7-Dihydroxy-4-methylcoumarin, formalin and dimethylamine on Mannich reaction gave a polymeric product.


OH
C6H5CH2NH2
CH2O
C6H5CH2N
(xi)
Piperidine
CH2O
OH
C6H5CH2NHCH2
(xii)
Sommelet reaction
NCH2
OH
(xiii)
Sommelet reaction
OH
CHO
Dakin oxidation
OH
OH

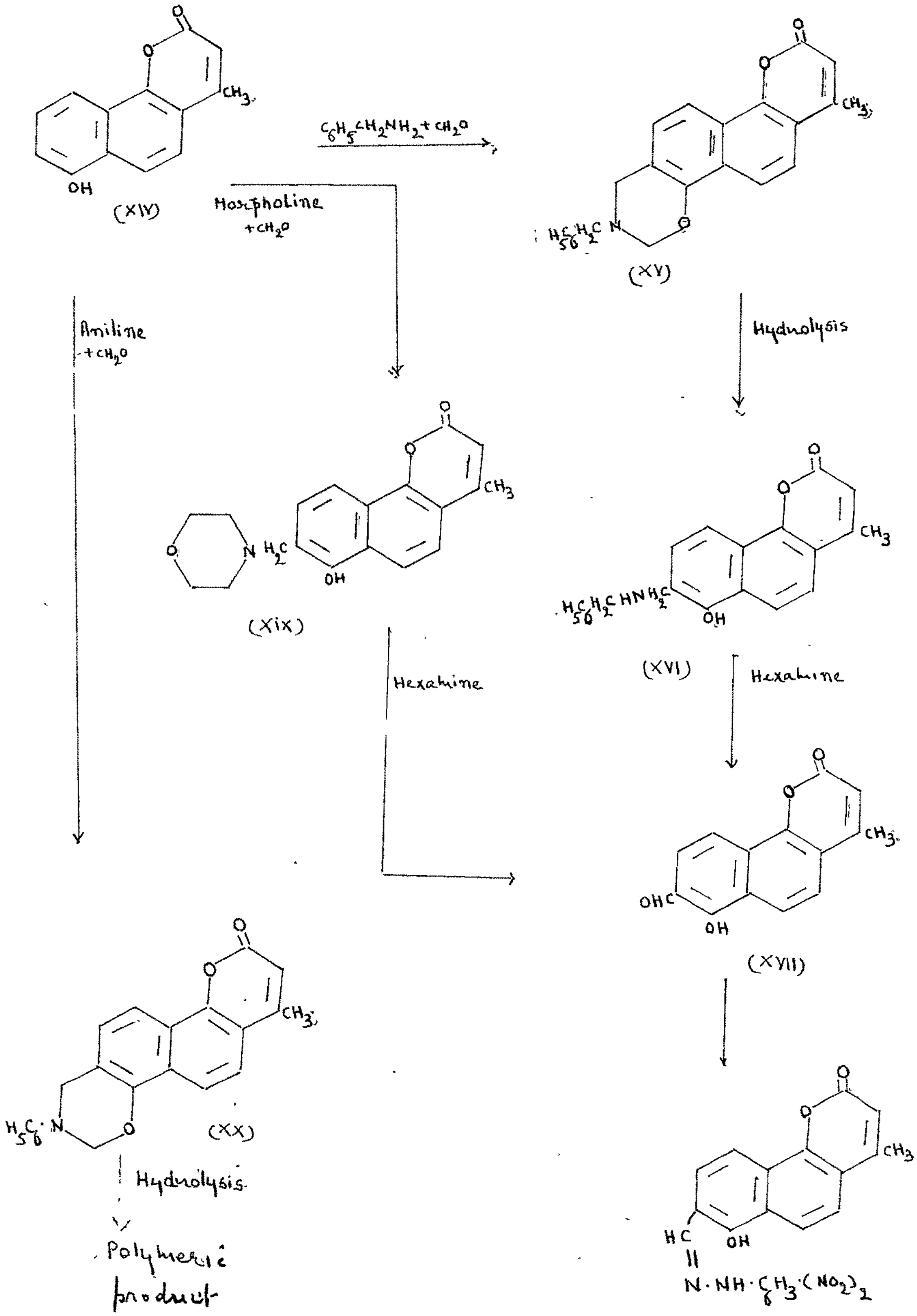
Mannich bases from 6'-hydroxy-4-methyl-7,8-benzocoumarin

6'-Hydroxy-4-methyl-7,8-benzocoumarin has been subjected to Mannich reaction with formalin and benzylamine, aniline and morpholine.

6'-Hydroxy-4-methyl-7,8-benzocoumarin(XIV), formalin and benzylamine in equi~~ll~~molecular quantities gave a compound to which 2'-H-3'-benzyl-3',4'-dihydro-1',3'-benzoxazino-(7',8',8,7)-4-methylcoumarin (XV) structure has been assigned as the product was insoluble in alkali and on treatment with alcoholic hydrochloric acid it gave formaldehyde and 6'-hydroxy-5'-benzylaminomethyl-4-methyl-7,8-benzocoumarin (XVI). This was further subjected to Sommelet reaction when 6'-hydroxy-5'-formyl-4-methyl-7,8-benzocoumarin (XVII) hither to unknown, was obtained which also prepared by direct formylation with hexamine. It gave light brown ferric chloride colouration and a 2,4-dinitrophenylhydrazone (XVIII). ~~was also prepared~~.

6'-Hydroxy-4-methyl-7,8-benzocoumarin ,formalim and morpholine in equimolecular quantities gave a compound to which the 6'-hydroxy-5'-morpholinomethyl-4-methyl-7,8-benzocoumarin (XIX) structure has been assigned because on treatment with hexamethylenetetramine it gave the 6'-hydroxy-5'-formyl-4-methyl-7,8-benzocoumarin described before as seen by direct comparison.

6'-Hydroxy-4-methyl-7,8-benzocoumarin, formalin and aniline gave ~~an~~ a ~~oxazino derivative~~ product which on hydrolysis gave a polymerised product, insoluble in common organic solvents. ~~It~~ The reaction product has been tentatively assigned 2'-H-3'-phenyl-3',4'-dihydro-1',3'-benzoxazino(7',8'-8,7)-4-methylcoumarin (XX) structure on the basis of the analytical results.


(XIV)
$C_6H_5CH_2NH_2 + CH_2O$
Morpholine + CH_2O
(XV)
Hydrolysis
Aniline + CH_2O
(XIX)
(XVI)
Hexamine
Hexamine
(XVII)
(XX)
Hydrolysis
Polymeric product
(XVIII)

The physiological activity of the Mannich bases prepared in the course of this work has not been studied so far but they are being sent for testing their physiological activity.

EXPERIMENTAL

Mannich reaction on 7,8-dihydroxy-4-methylcoumarin with formalin and dimethylamine : 7,8-Dihydroxy-6-dimethylaminomethyl-4-methylcoumarin

7,8-Dihydroxy-4-methylcoumarin (1.92 g.) dimethylamine (1 ml.) and formalin (0.6 ml.) were refluxed in alcohol on a water bath for 2 hr. The product obtained was crystallised from alcohol. M.P. 221-23°.

Analysis : Found : C=62.2 % ; H=6.0 % ; N=5.5 %.

$C_{13}H_{15}O_4N$ requires : C=62.6 % ; H=6.0 % ; N=5.6 %.

Sommelet reaction on 7,8-dihydroxy-6-dimethylaminomethyl-4-methylcoumarin

The above Mannich base (1 g.) was refluxed with acetic acid (10 ml.) and hexamethylene tetramine (2 g.) for 4 hours on a wire gauze on a low flame. Concentrated hydrochloric acid (10 ml.) was added and the mixture was refluxed further for one hour. It was then added to water (500 ml.) and the solution was extracted with ether. The residue obtained on removal of ether crystallised from benzene in yellowish white needles, which was found to be identical with 7,8-dihydroxy-6-formyl-4-methylcoumarin (loc.cit) obtained from formylation of 7,8-dihydroxy-4-methylcoumarin.

Mannich reaction on 7,8-dihydroxy-4-methylcoumarin with formalin and piperidine : 7,8-Dihydroxy-6-piperidinomethyl 4-methylcoumarin

7,8-Dihydroxy-4-methylcoumarin (1.92 g.) in methanol, formalin (0.3 g.) and piperidine (0.85 g.)were heated on a water bath for 2 hr. The residue obtained after recovering the solvent was washed with benzene and crystallised from benzene - methanol mixture; m.p.195-7°.

Analysis : Found : C=66.2 % ; H=6.4 % ; N=4.8 %.

$C_{16}H_{19}O_4N$ requires : C=66.4 % ; H=6.6 % ; N=4.8 %.

Sommelet reaction on 7,8-dihydroxy-6-piperidinomethyl 4-methylcoumarin

7,8-Dihydroxy-6-piperidinomethyl-4-methylcoumarin (1 g.) was refluxed with acetic acid (10 ml.) and hexamethylene tetramine (1 g.) for 4 hours on a wire gauze on a low flame. The reaction mixture on heating with concentrated hydrochloric acid and working up as before gave 7,8-dihydroxy-6-formyl-4-methylcoumarin described before.

Mannich reaction on 7,8-dihydroxy-4-methylcoumarin with formalin and morpholine : 7,8-Dihydroxy-6-morpholinomethyl 4-methylcoumarin

To formalin (2 ml.) in absolute ethanol (10 ml.) morpholine (1 ml.) was added followed by 7,8-dihydroxy-4-methylcoumarin (1.92 g.) and absolute alcohol (5 ml.). The reaction mixture was gently refluxed on a steam bath for 2 hours and then left over-night. The residue remaining after removal of alcohol was extracted with cold benzene and the solid obtained from the benzene extract crystallised from benzene-petroleum ether mixture in yellow needles, m.p. 193-4°.

Analysis : Found : C=62.0 % ; H=5.7 % ; N=4.4 %.

$C_{15}H_{17}O_5N$ requires : C=61.8 % ; H=5.8 % ; N=4.8 %.

Sommelet reaction on 7,8-dihydroxy-6-morpholinomethyl-4-methylcoumarin

The above base (0.5 g.) was refluxed with acetic acid (10 ml.) and hexamethylene tetramine (1 g.) for 4 hours on a wire gauze on a low flame. The reaction mixture on heating with concentrated hydrochloric acid and working up as before gave 7,8-dihydroxy-6-formyl-4-methylcoumarin described before.

Mannich reaction on 5-hydroxy-4-methylcoumarin : 2'H-3'-benzyl-3',4'-dihydro-1',3'-oxazino-(5',6'-6,5)-coumarin

Formalin (0.6 ml.) was dissolved in absolute alcohol (5 ml.) . Benzylamine (1 ml.) was added gradually with cooling followed by 5-hydroxy-4-methylcoumarin (1.76 g.) and absolute alcohol (5 ml.). The reaction mixture was gently refluxed on a steam bath for 2 hours. The product went in solution within fifteen minutes and then bright shining brown needles separated. The product collected after keeping the reaction mixture at room temperature over-night crystallised from benzene in needles, m.p. 143-4°.

Analysis : Found : C=74.6 % ; H=5.2 % ; N=4.3 %.
$C_{19}H_{17}O_3N$ requires: C=74.2 % ; H=5.5 % ; N=4.5 %.

The above product was soluble in concentrated hydrochloric acid and insoluble in sodium hydroxide.

5-Hydroxy-6-benzylaminomethyl-4-methylcoumarin

The above oxazine (1.4 g.) was added gradually to ethyl alcohol (10 ml.) and concentrated aqueous hydrochloric acid (5 ml.). The resulting solution was distilled on a wire gauze and the distillate collected in water (25 ml.). During the course of distillation dilute alcohol (20 ml.), 1 : 1 by volume) was added and the distillation was stopped when a solid began to separate out in the distilling flask. It was dissolved by addition of more ethanol. The resulting solution was just neutralised by addition of saturated solution of sodium bicarbonate. The solid obtained crystallised from benzene-petroleum ether in needles, m.p. 186-7°.

Analysis : Found : C=72.8 % ; H=5.8 % ; N=4.6 %.

$C_{18}H_{17}O_3N$ requires: C=73.2 % ; H=5.7 % ; N=4.7 %.

Mannich reaction on methyl-5-hydroxy-4-methylcoumarin-6-carboxylate : Methyl-5-hydroxy-8-dimethylaminomethyl-4-methylcoumarin-6-carboxylate

Methyl-5-hydroxy-4-methylcoumarin-6-carboxylate (2.34 g.), dimethylamine (1 ml.) and formalin (1 ml.) were heated together in alcohol for 2 hours on a steam bath. The paste obtained was dried and washed with petrol and benzene. The residue was crystallised from absolute alcohol ; m.p. 120-1°.

Analysis : Found : C=62.1 % ; H=5.3 % ; N=4.6 %.

$C_{15}H_{17}O_5N$ requires: C=62.0 % ; H=5.5 % ; N=4.8 %.

Methyl-5-acetoxy-8-acetoxymethyl-4-methylcoumarin-6-carboxylate

The above product (0.2 g.) was refluxed with sodium acetate and acetic anhydride (0.5 g.). The reaction mixture was poured on ice and the separated product crystallised from benzene in white needles, m.p. 158-60°.

Analysis : Found : C=58.4 % ; H=4.2 %.

$C_{17}H_{16}O_8$ requires: C=58.6 % ; H=4.5 %.

The same acetylated product was obtained by the acetylation of methyl-5-hydroxy-8-chloromethyl-4-methylcoumarin-6-carboxylate.

Mannich reaction on 8-hydroxycoumarin with formalin and benzylamine : 2'H-3'-benzyl-3',4'-dihydro-1',3'-oxazino-5',6'-7,8-coumarin

Formalin (0.6 ml.) was dissolved in absolute alcohol (5 ml.), benzylamine (1 ml.) was added gradually with cooling followed by 8-hydroxycoumarin (1.62 g.) and absolute alcohol (5 ml.). The reaction mixture was gently refluxed on a steam bath for 2 hours. The product went in solution within ten minutes and then bright shining yellow needles separated. The product collected after keeping the reaction mixture at room temperature over-night crystallised from benzene in needles, m.p. 186-7°.

Analysis : Found : C=74.0 % ; H=5.0 % ; N=4.4 %.

$C_{18}H_{15}O_3N$ requires: C=73.7 % ; H=5.1 % ; N=4.7 %.

The above product was soluble in concentrated hydrochloric acid and insoluble in sodium hydroxide.

8-Hydroxy-7-benzylaminomethylcoumarin

The above oxazino derivative (1.4 g.) was added gradually to ethyl alcohol (10 ml.) and concentrated aqueous hydrochloric acid (5 ml.). The resulting solution was distilled on a wire gauze and the distillate collected in water (25 ml.). During the course of distillation dilute alcohol (20 ml. ; 1 : 1 by volume) was added and the distillation was stopped when a solid began to separate out in the distilling flask. It was dissolved by addition of more ethanol. The resulting solution was just neutralised by addition of saturated solution of sodium bicarbonate. The solid obtained crystallised from benzene-petroleum ether in needles, m.p. 143-4°.

Analysis : Found : C=72.3 % ; H=5.3 % ; N=4.8 %.
$C_{17}H_{15}O_3N$ requires : C=72.6 % ; H=5.3 % ; N=4.9 %.

Sommelet reaction on 8-hydroxy-7-benzylaminomethylcoumarin

The above Mannich base (2.6 g.) and hexamethylenetetramine (5.6 g.) in glacial acetic acid were heated for 6 hrs. on a steam bath and then hydrochloric acid (Conc. 15 ml.) was added and the heating continued for 2 hrs. The product obtained on ether extraction crystallised from glacial acetic acid, m.p. 238-40°. Mixed m.p. with 8-hydroxy-7-formylcoumarin was not depressed.

Mannich reaction on 8-hydroxycoumarin with formalin and piperidine : 8-Hydroxy-7-piperidinomethylcoumarin

A mixture of formalin (0.3 g.), piperidine (0.85 g.) and 8-hydroxycoumarin (1.62 g.) was refluxed in alcohol (5 ml.) on a water bath for 2 hours. The reaction mixture was then evaporated to dryness. The paste obtained was treated first with petrol and then with benzene and the residue crystallised from benzene-methanol mixture in needles, m.p. 148-50°.

Analysis : Found : C=69.7 % ; H=6.5 % ; N=5.4 %.
$C_{15}H_{17}O_3N$ requires : C=69.5 % ; H=6.6 % ; N=5.5 %.

Sommelet reaction on 8-hydroxy-7-piperidinomethylcoumarin

The above Mannich base on refluxing with glacial acetic acid and hexamine for 4 hours, on a water bath, on working up as usual gave a residue which was crystallised from acetic acid in yellow needles, m.p. 238-9°. Mixed m.p. with 8-hydroxy-7-formylcoumarin ~~and this product~~ was ~~did~~ not depressed.

Mannich reaction on 6'-hydroxy-4-methyl-7,8-benzocoumarin: 2'-H-3'-benzyl-3',4'-dihydro-1',3'-benzoxazino-(7',8'-8,7)-4-methylcoumarin

Formalin (0.6 ml.) was dissolved in alcohol (5 ml.). Benzylamine (1 ml.) was added gradually with cooling followed by 6'-hydroxy-4-methyl-7,8-benzocoumarin (2.6 g.) in alcohol. The reaction mixture was gently refluxed on a steam bath for 2 hrs. The product went in solution within 10 minutes and then bright shining yellow plates separated out. The product collected after keeping the reaction mixture at room temperature overnight crystallised from benzene-petrol mixture in needles, m.p. 208-09°.

Analysis : Found : C = 77.6 % ; H = 5.6 % ; N=3.8 %.
$C_{23}H_{19}O_3N$ requires C= 77.3 % ; H = 5.3 % ; N = 3.9 %

6'-Hydroxy-5'-benzylaminomethyl-4-methyl-7,8-benzocoumarin

The above oxazine derivative (1 g.) was added gradually to ethyl alcohol (10 ml.) and con.hydrochloric acid (1 : 1). The resulting solution was distilled on a wire gauze and the distillate collected (25 ml.). During the course of distillation dilute alcohol (1 : 1 ; 20 ml.) was added and the distillation was stopped when solid began to separate out in the distilling flask. It was just neutralised by addition of saturated solution of sodium bicarbonate. The solid obtained crystallised from benzene-petrol mixture in white tufts, m.p. 160°.

Analysis : Found : C = 76.4 % ; H= 5.4 % ; N=3.8%.

$C_{22}H_{19}O_3N$ requires : C = 76.5 % ; H = 5.5 % ; N=4.0%.

Sommelet reaction on 6'-hydroxy-5'-benzylaminomethyl-4-methyl-7,8-benzocoumarin : 6'-Hydroxy-5'-formyl-4-methyl-7,8-benzocoumarin

The above Mannich base (2 g.) and hexamethylenetetramine (5.6 g.) in glacial acetic acid were heated for 4 hrs. on a steam bath and then hydrochloric acid (conc.15 ml.) was added and the heating continued for 2 hrs. The product obtained on ether extraction was crystallised from acetic acid in yellow needles, m.p. 265-66°.

Analysis : Found : C = 68.5 % ; H = 3.5 %.

$C_{15}H_{10}O_4 \cdot 1/2\ H_2O$ requires : C = 68.4 % ; H = 3.5 %.

The 2,4-dinitrophenyl hydrazone

2,4-Dintrophenyl hydrazine (0.1 g.) was dissolved in glacial acetic acid and then added to 6'-hydroxy-5'-formyl-4-methyl-7,8-benzocoumarin (0.1 g.) in glacial acetic acid. The mixture was refluxed for 30 minutes when 2,4-dinitrophenylhydrazone separated out. It was insoluble in all common organic solvents. It crystallised from nitrobenzene in needles, m.p. 295-97°.

Analysis : Found : N = 13.5 %.

$C_{21}H_{14}O_7N_4$ requires : N = 12.9 %.

Mannich reaction on 6'-hydroxy-4-methyl-7,8-benzocoumarin: with formalin and morpholine : 6'-Hydroxy-5'-morpholinomethyl-4-methyl-7,8-benzocoumarin

A mixture of formalin (0.3 g.) morpholine (0.87 g.) and 6'-hydroxy-4-methyl-7,8-benzocoumarin (2.6 g.) was refluxed in alcohol (5 ml.) on a water bath for 2 hours. The mixture ~~gets~~ became clear after ten minutes and the product separated recrystallised from benzene-petrol mixture as white plates, m.p. 200°.

Analysis : Found : C = 69.9 % ; H = 5.5 % ; N=4.1 %

$C_{19}H_{19}O_4N$ requires : C = 70.1 % ; H = 5.9 % ; N=4.3 %

Sommelet reaction on 6'-hydroxy-5'-morpholinomethyl-4-methyl-7,8-benzocoumarin

The above Mannich base ~~ea~~ was reflux~~ing~~ed with glacial acetic acid and hexamine for 4 hrs. on a water bath. It was decomposed by hydrochloric acid (1 : 1). On working up as usual gave a residue which was crystallised from acetic acid in yellow plates, m.p. 265-66°. Mixed m.p. with 6'-hydroxy-5'-formyl-4-methyl-7,8-benzocoumarin described earlier was not depressed.

Mannich reaction on 6'-hydroxy-4-methyl-7,8-benzocoumarin with aniline : 2'-H-3'-phenyl-3',4'-dihydro-1',3'-benzoxazino-(7',8'-8,7)-4-methylcoumarin

6'-Hydroxy-4-methyl-7,8-benzocoumarin (2.6 g.) was dissolved in alcohol and aniline (1 ml.) was then added to it and cooled. This was followed by formalin

(0.7 ml.) and the reaction mixture was gently refluxed on a water bath for 2 hrs. The product separated was crystallised from benzene, m.p. 201-02°.

Analysis : Found : C = 77.5 % ; H = 4.9 % ; N=3.9 %
$C_{22}H_{17}O_3N$ requires : C = 77.0 % ; H = 5.0 % ; N=4.0 %

On hydrolysis the above base gave a polymeric product which was insoluble in all organic solvents and had a very high melting point,

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