CHAPTER V

MANNICH REACTION ON SOME HYDROXYCOUMARINS

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A reaction first described by the German Chemist Carl Mannich in 1917 involves the condensation of a compound containing acidic hydrogen with an aldehyde, usually formaldehyde and ammonia or a primary amine or secondary amine.

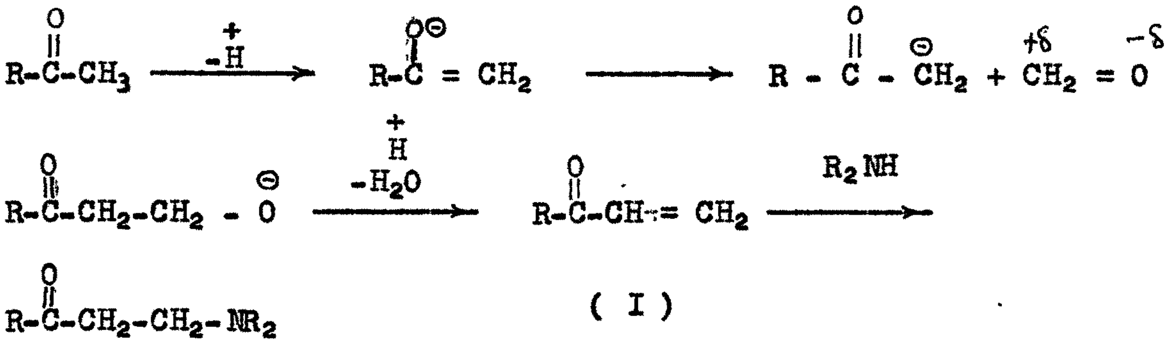
$$B : H + CH_2O + NHRR' \longrightarrow BCH_2NRR' + H_2O$$

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.

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 (J. Am. Chem. Soc., 1949, 71, 609) 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 depolymerization of paraformaldehyde. The time 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 reactions of phenols with formaldehyde and primary amines the reaction is generally complete in about two hours time. In the case of a few ketones, it is found that the reaction may be complete within a few minutes of refluxing.

Mechanism of the Mannich Reaction

Dalgliesh (J. Am. Chem. Soc., 1949, 71, 1697) suggested a mechanism which involves formation of an α-β-unsaturated ketone (I) that adds ammonia.

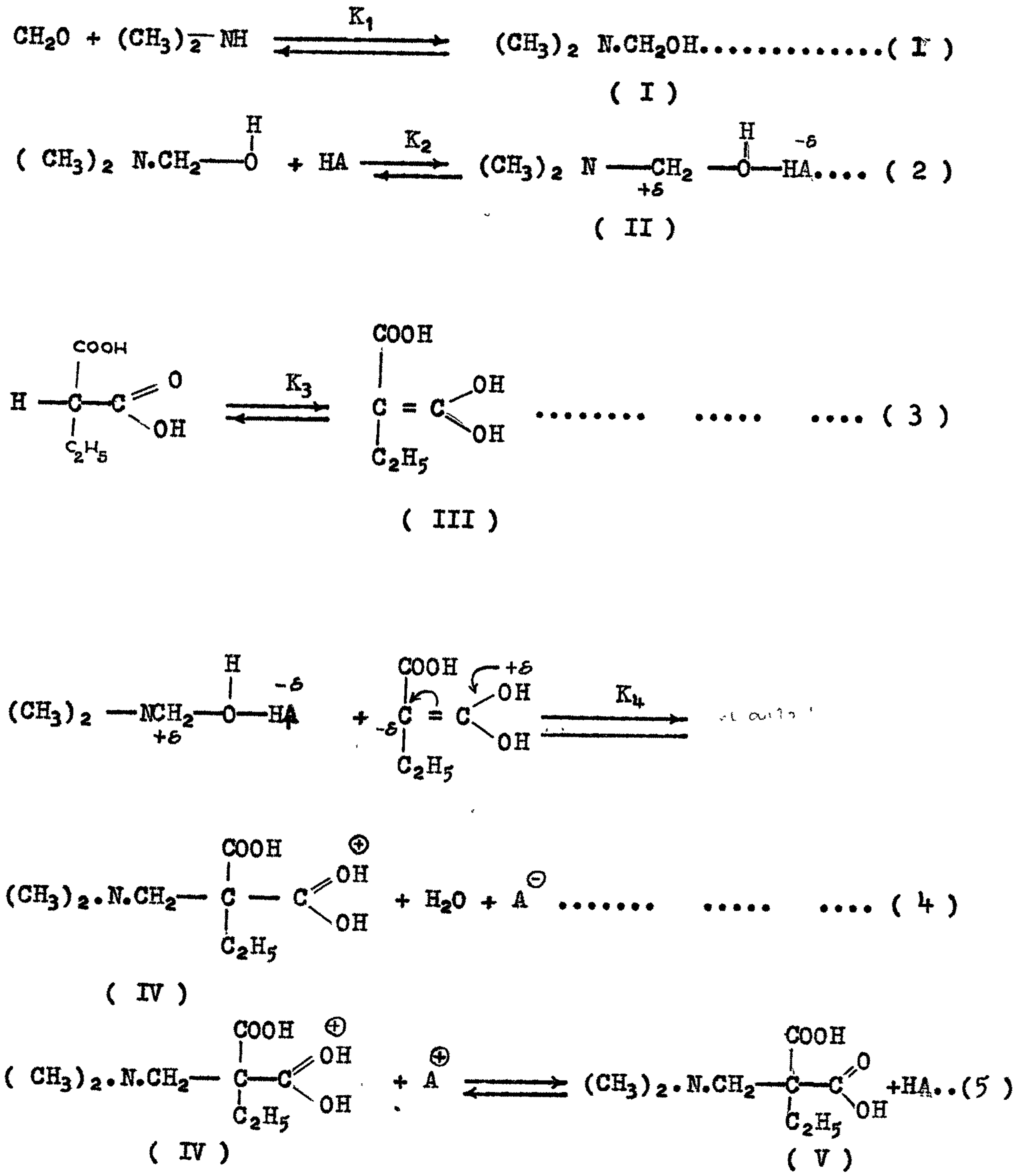


$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3 \xrightarrow{\overset{+}{-H}} R\text{-}\overset{O^{\ominus}}{\overset{|}{C}} = CH_2 \longrightarrow R - \overset{O}{\overset{\|}{C}} - \overset{\ominus}{C}H_2 + \overset{+\delta}{C}H_2 = \overset{-\delta}{O}$$

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

(I)

Quite a different mechanism was proposed by Alexander et al. (J. Am. Chem. Soc., 1949, 71, 4014) for the reaction of compounds containing active methy myl 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 (I). 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 $A^{\ominus}$ and a protonated molecule of dimethylaminomethyl malonic acid (IV). Reaction of the protonated molecule with the conjugate base $A^{\ominus}$ would give the free amino acid (V).



$$CH_2O + (CH_3)_2NH \xrightleftharpoons{K_1} (CH_3)_2N.CH_2OH \quad \ldots\ldots\ldots\ldots (1)$$

(I)

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

(II)

$$H-\overset{COOH}{\overset{|}{\underset{\underset{C_2H_5}{|}}{C}}}-C\begin{matrix}=O\\ \diagdown OH\end{matrix} \xrightleftharpoons{K_3} \overset{COOH}{\overset{|}{\underset{\underset{C_2H_5}{|}}{C}}}=C\begin{matrix}\diagup OH\\ \diagdown OH\end{matrix} \quad \ldots\ldots\ldots \quad \ldots\ldots \quad \ldots\ldots (3)$$

(III)

$$(CH_3)_2-\underset{+\delta}{NCH_2}-\overset{H}{\overset{|}{O}}-\overset{-\delta}{HA} + \overset{COOH}{\overset{|}{\underset{\underset{C_2H_5}{|}}{{}_{-\delta}C}}}=C\begin{matrix}\diagup OH^{+\delta}\\ \diagdown OH\end{matrix} \xrightleftharpoons{K_4}$$

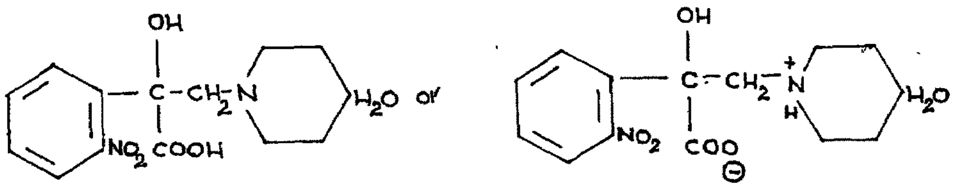
$$(CH_3)_2.N.CH_2-\overset{COOH}{\overset{|}{\underset{\underset{C_2H_5}{|}}{C}}}-C\begin{matrix}\overset{\oplus}{=OH}\\ \diagdown OH\end{matrix} + H_2O + A^{\ominus} \quad \ldots\ldots\ldots \quad \ldots\ldots \quad \ldots\ldots (4)$$

(IV)

$$(CH_3)_2.N.CH_2-\overset{COOH}{\overset{|}{\underset{\underset{C_2H_5}{|}}{C}}}-C\begin{matrix}\overset{\oplus}{=OH}\\ \diagdown OH\end{matrix} + A^{\oplus} \xrightleftharpoons{} (CH_3)_2.N.CH_2-\overset{COOH}{\overset{|}{\underset{\underset{C_2H_5}{|}}{C}}}-C\begin{matrix}=O\\ \diagdown OH\end{matrix} + HA\ldots(5)$$

(IV) (V)

The postulation of enolization step (3), in the above mechanism was questioned by Grillot et al. (J. Am. Chem. Soc., 1950, 72, 2813 ; 73, 5598). 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 r~~e~~acimization rendered inadmissible the enolization step postulated above. However, this objection has been cleared by the excellent work of Meinwald et al. (J. Am. Chem. Soc., 1953, 75, 485) 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.



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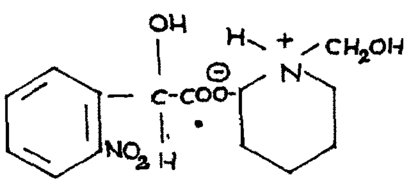
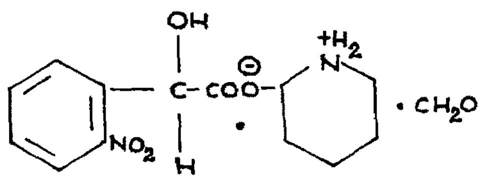


II



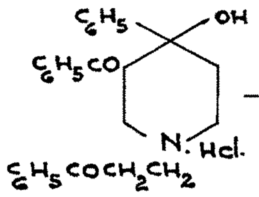
III

Lieberman and Wagner (J. Org. Chem., 1949, 14, 1011) believe that the Mannich reaction involves a dual catalysis in an amphoteric system in which the cation $R_2 N - C^{+}-$ 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.

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 (Ber., 1935, 68, 113) obtained a substituted piperidine from acetophenone, formaldehyde and ammonium chloride.



$$\longrightarrow (C_6H_5COCH_2CH_2)_3\ N.HCl$$

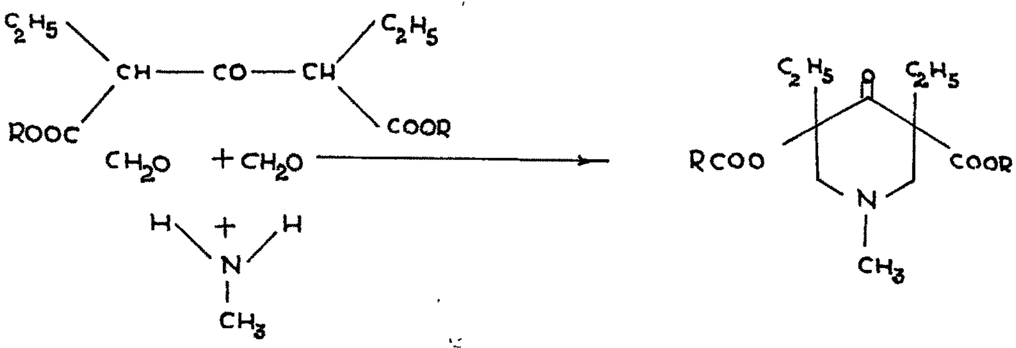
The piperidine derivative readily changes to the salt of tri- (β-benzoyl ethyl) amine.

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

A number of acids and esters containing highly active 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 some times takes place. In the Mannich reaction of acids with primary amines the first product often undergoes further condensation to form a tertiary amine. When a primary amine is used with a poly carbonyl compound which contains reactive hydrogen atoms on carbon atoms located in the 1,3-position with respect to each other, then pyridones may be expected, for example

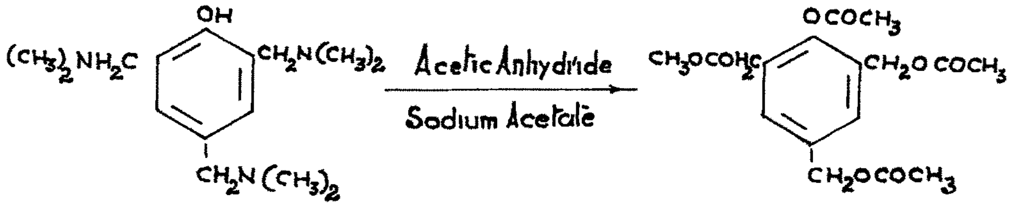


If the pyridon contains hydrogen atom on the 3 and 5 position the condensation may be carried out one step further and a bicyclic ring system Bispidin is produced.

Reaction with phenols

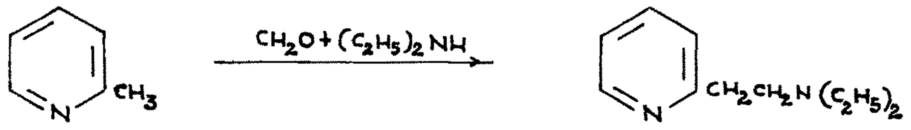
Decombe (Compt. rend., 1933, 196, 866) conclusively proved that in the condensation of a phenol with formaldehyde and secondary amines the resulting dialkylamino methyl group enters the ortho or para position or both and that in no case it attaches to oxygen of the hydroxyl group.

Brusson and co-workers (J. Am. Chem. Soc., 1941, 63, 270) showed that when phenolic Mannich bases were treated with acetic anhydride their dimethylaminomethyl groups were replaced by Acetoxy methyl groups.

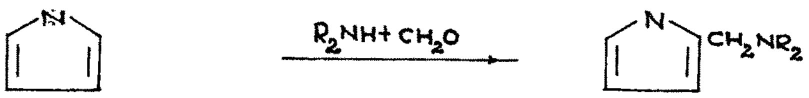


Reaction with heterocyclic compounds

A number of heterocyclic systems containing nitrogen oxygen or sulphur have been studied. In the systems containing nitrogen atom such as α-picolines and quinaldines, the hydrogen of the α-methyl group is sufficiently reactive to take part in the Mannich reaction. Thus Tseou and co-workers (Compt. rend., 1931, 192, 1242) found that the condensation of α-picoline with formaldehyde and dimethylamine gave 2-(β-diethylaminomethyl) pyridine.



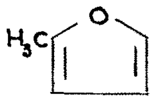
Mannich reaction with pyrrole has been studied by a number of workers. Hydrogen on α-carbon atom was substituted but the resulting Mannich bases being unstable, they were characterized by their picrates.

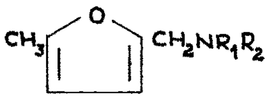


N-Ethyl and N-methyl pyrrole do not undergo Mannich reaction.

Burke and co-workers (J. Am. Chem. Soc., 1954, 76, 1294) have reported the reaction of several pyrroles with formaldehyde and primary amines.

Nixon and co-workers (J. Am. Chem. Soc., 1946, 68, 1198) subjected 2-methyl furan to Mannich reaction using formaldehyde and primary and secondary amines. In all cases the expected Mannich bases furfurylamines (I) or (II) or their hydrochlorides were obtained. The reaction was shown to be taking place in the α-position.





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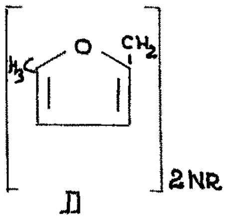


II

Wiley (J. Am. Chem. Soc., 1951, 73, 4205 ; 1952, 74, 4326 ; C.A. 10011 d) studied 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) chromone hydrochlorides. The above reaction in case of series of 2-methylchromones failed.

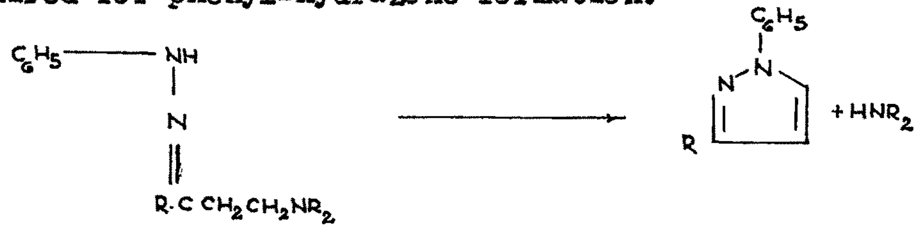
P.Da Re. et al. (Nature, 1959, 184, 362 ; J. Org. Chem., 1960, 25, 1097) studied the Mannich reaction on 7-hydroxy-2,3-dimethyl-, 2-methyl-3-ethyl-, 2-ethyl-3-methyl-chromones with dimethylamine, diethylamine, morpholine and piperidine and formalin and obtained the corresponding 8-dimethyl aminomethylchromones. Similar results were obtained in 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.

The application of Mannich reaction

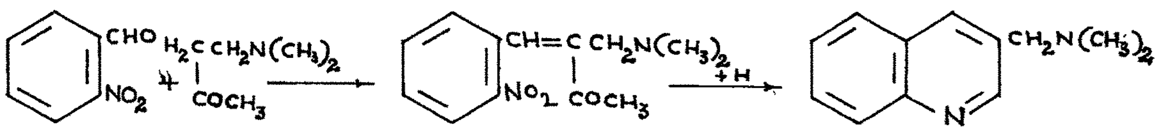
In recent years, the Mannich reaction has proved to be a formidable tool in synthetic organic chemistry. The products obtained in the Mannich reaction may be further converted into a variety of compounds. A few of these may be mentioned here. Some of the Mannich bases and their reduction products have proved to be important medicinal agents.

The most 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 an ethylenic substance.

The phenyl hydrazones of ketonic bases form pyrazolines by internal amine exchange under conditions similar to those required for phenyl-hydrazone formation.

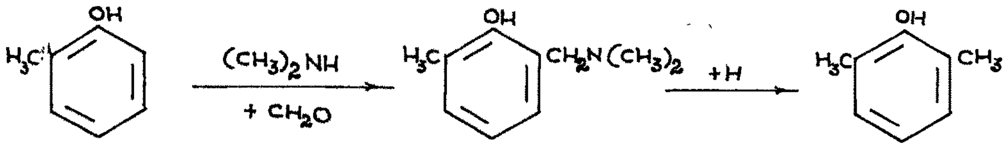


Mannich et al. (Arch. Pharm., 1933, 271, 116) found that β-dimethylaminomethyl ketone and o-nitrobenzaldehyde, reacted to give a product which upon reduction lost water to form a substituted quinoline.



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 (J. Am. Chem. Soc., 1939, 61, 765) have developed a new method for nuclear methylation of phenols which consists in the hydrogenolysis of the dimethylaminomethyl derivative obtained by Mannich reaction. Using this method Callin et al. (J. Am. Chem. Soc., 1950, 72, 2763) achieved a practical synthesis of 2,6-xylenol.



Synthesis of piperidines and piperidones : Piperidines are obtained from condensation products from one mole of a primary amine two moles of formaldehydes and two moles of ketones.

Conversion of Mannich bases into aldehydes : Synder (J. Am. Chem. Soc., 1952, 74, 5110)observed that when Mannich base in acetic acid solution was treated with hexamethylene tetramine the intermediate quaternary salt decomposed to an aldehyde. Thus

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

$$(CH_3)_2NH + RCH_2-N(CH_2)_6N_3^{+} + CH_3COO^{-}$$

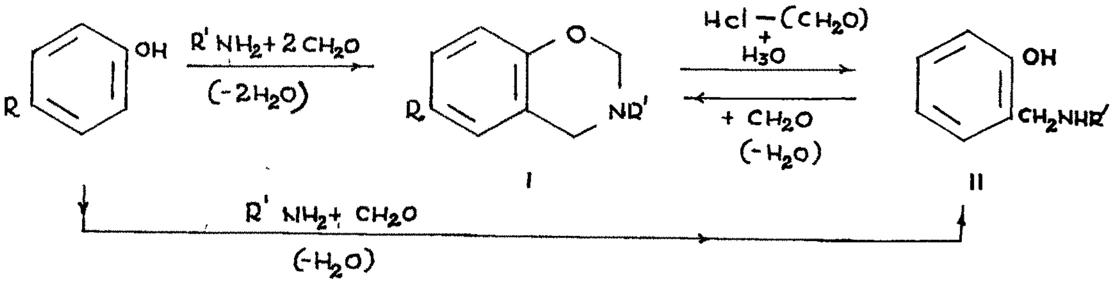
$$RCH_2N(CH_2)_6N_3^{+} \longrightarrow RCHO$$

The intermediate quaternary salts were of the type encountered in the Sommelet synthesis (Sommelet, Compt. rend., 1913, 157, 852). The conversion of primary and secondary amines to aldehydes by modified Sommelet reaction was described by Graymore et al. (J. Chem. Soc., 1945, 293). One of the most fruitful application of a number of Mannich bases and their quaternary salts is their ability to C-alkylate substances that can readily form anions. Generally tertiary amines and their quaternary salts which can be prepared from ketones, phenols, heterocyclic compounds and nitrocompounds by Mannich reaction are capable of engaging in carbon-carbon alkylation with active methylene compound and their sodio derivatives, alkalicyanides, and organo metallic compounds. All these alkylation are described by Brewster and co-workers (Organic Reactions, 1952, Vol. 7, 99-196).

Synthesis of 1,3-Oxazine derivatives :

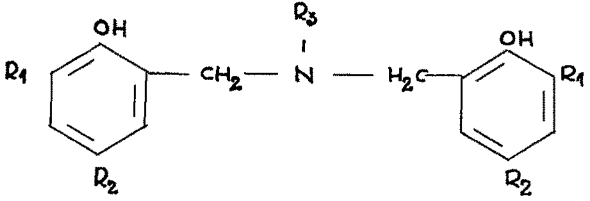
Although the reaction of phenols with formaldehyde and secondary amines have been extensively studied, analogous studies involving primary amines appear to have been limited to the use of 2-aminoethanol. (Bruson J. Am. Chem. Soc., 1936, 58, 1741) before the related work of Burke and co-workers. Reactions of equimolecular quantitites of this amine with formaldehyde and certain ortho and para substituted phenols resulted in crystalline compounds having ortho or para β-hydroxy ethylaminomethyl groups.

Burke (J. Am. Chem. Soc., 1949, 71, 609) showed that whereas the condensation of equimolecular quantities of parasubstituted phenols with formaldehyde and primary amines gave o-alkylaminomethyl-p-substituted phenols, when the reaction was carried out using phenol~~s~~, formaldehyde and primary amine~~s~~ in a molar ratio of 1:2:1 respectively ~~resulted in~~ the formation of substituted benzoxazine (I) a new series of compounds, took place.



These benzoxazines could be prepared alternatively 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. These benzoxazine derivatives on heating with hydrochloric acid in alcoholic solution decompose readily to give formaldehyde and the corresponding o-alkylaminomethyl-p-substituted phenols.

Burke and co-workers (J. Am. Chem. Soc., 1952, 74, 602) showed that a third kind of product N,N-bis-(2-hydroxybenzyl)-alkylamines (III) could be directly obtained in the reaction of certain ortho para substituted phenols with formaldehyde and primary amines.

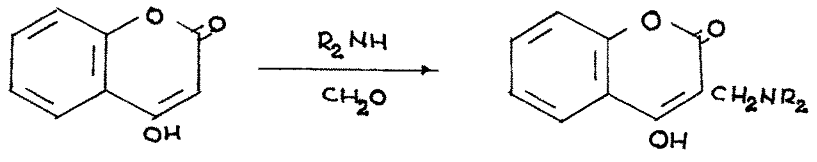


III

Burke and Weatherbee (J. Am. Chem. Soc., 1950, 72, 4691 ; 1952, 74, 3601) found that when polyhydroxyphenols were condensed with formaldehyde and primary amines poly-1,3-benzoxazines were ~~found~~ formed. β-naphthol and α-naphthol with formaldehyde and primary amines in a molar ratio of 1:2:1 respectively gave the corresponding naphthoxazino derivatives.

* * *

There is only one instance in literature of the application of Mannich reaction to coumarin derivatives. Robertson and Link (J. Am. Chem. Soc., 1953, 75, 1883) reported the preparation of a series of 3-substituted aminomethyl-4-hydroxycoumarins (II) from 4-hydroxycoumarin (I) formaldehyde and different primary and secondary amines.

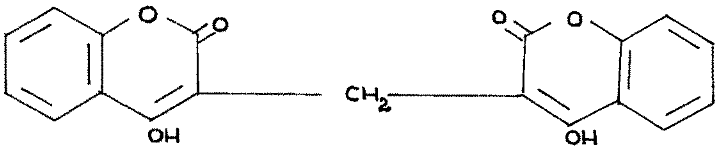


I

II

These Mannich bases were assigned 3-substituted aminomethyl-4-hydroxycoumarin structures because of the known reactivity of the 3-position in 4-hydroxycoumarin.

The secondary amines other than dimethylamine and piperidine gave only the amine salts of dicoumarol. These salts on treatment with mineral acids readily gave dicoumarol (III). Dimethylamine and piperidine gave normal products.



III

The present work deals with the application of the Mannich reaction to 7-hydroxycoumarin and its derivatives and to 6-hydroxycoumarin. These have been condensed with dimethylamine aniline and benzylamine. Primary amines were particularly selected because of the interesting results obtained by Burke and co-workers (J. Am. Chem. Soc., 1949, <u>71</u>, 609) which have been discussed earlier.

The condensation was studied in most cases using three different molecular proportions of formaldehyde viz. 1 and 2 moles and excess. When the coumarin derivative, formaldehyde and the amine were in equimolecular proportions, the corresponding alkylaminomethyl derivatives of coumarins were obtained. With primary amines when 2 moles of formaldehyde were used the formation of an 1,3-oxazine derivative was observed in most of the cases wherever the reaction took place.

Mannich reaction on 7-hydroxycoumarin (chart on p.151)

7-Hydroxycoumarin (IV),formaldehyde and dimethylamine in equimolecular quantities gava a compound to which 7-hydroxy-8-dimethylaminomethylcoumarin (X) structure has been assigned because on treatment with hexamethylene tetramine it gave the known 7-hydroxy-8-formylcoumarin (VII) (Spath and Pailer, Ber., 1935, 68, 941) as seen by direct comparison. On treatment with acetic anhydride and sodium acetate (X) yielded 7-acetoxy-8-acetoxymethylcoumarin (XI).

7-Hydroxycoumarin when treated with formaldehyde and benzylamine in equimolecular proportions gave two products (A) and (B). The product (A) obtained in poor yield has been assigned 7-hydroxy-8-benzylaminomethylcoumarin structure (IX) as on treatment with hexamethylene tetramine in acetic acid it yielded the known 7-hydroxy-8-formylcoumarin (VII).

The product (B) which was obtained in better yield was also obtained when 7-hydroxycoumarin was treated with formaldehyde and benzylamine in the molar ratio of (1 : 2 : 1). It has been assigned 2'H-3'-benzyl-3',4'-dihydro-1',3'-oxazino-5',6',8,7-coumarin (VIII) structure. This structure has been assigned as the product was insoluble in alkali,and on treatment with alcoholic hydrochloric acid it gave formaldehyde and 7-hydroxy-8-benzylaminomethylcoumarin (IX) described above. The work of Burke (loc.cit.) on the formation of such compounds from phenols has already been discussed.

The formation of 8-substituted compounds in all these cases and the closing of the 1,3-oxazine ring between 7- and 8-positions is as expected from the behaviour of 7-hydroxycoumarin in various other reactions discussed in the General Introduction (See pages 14-27).

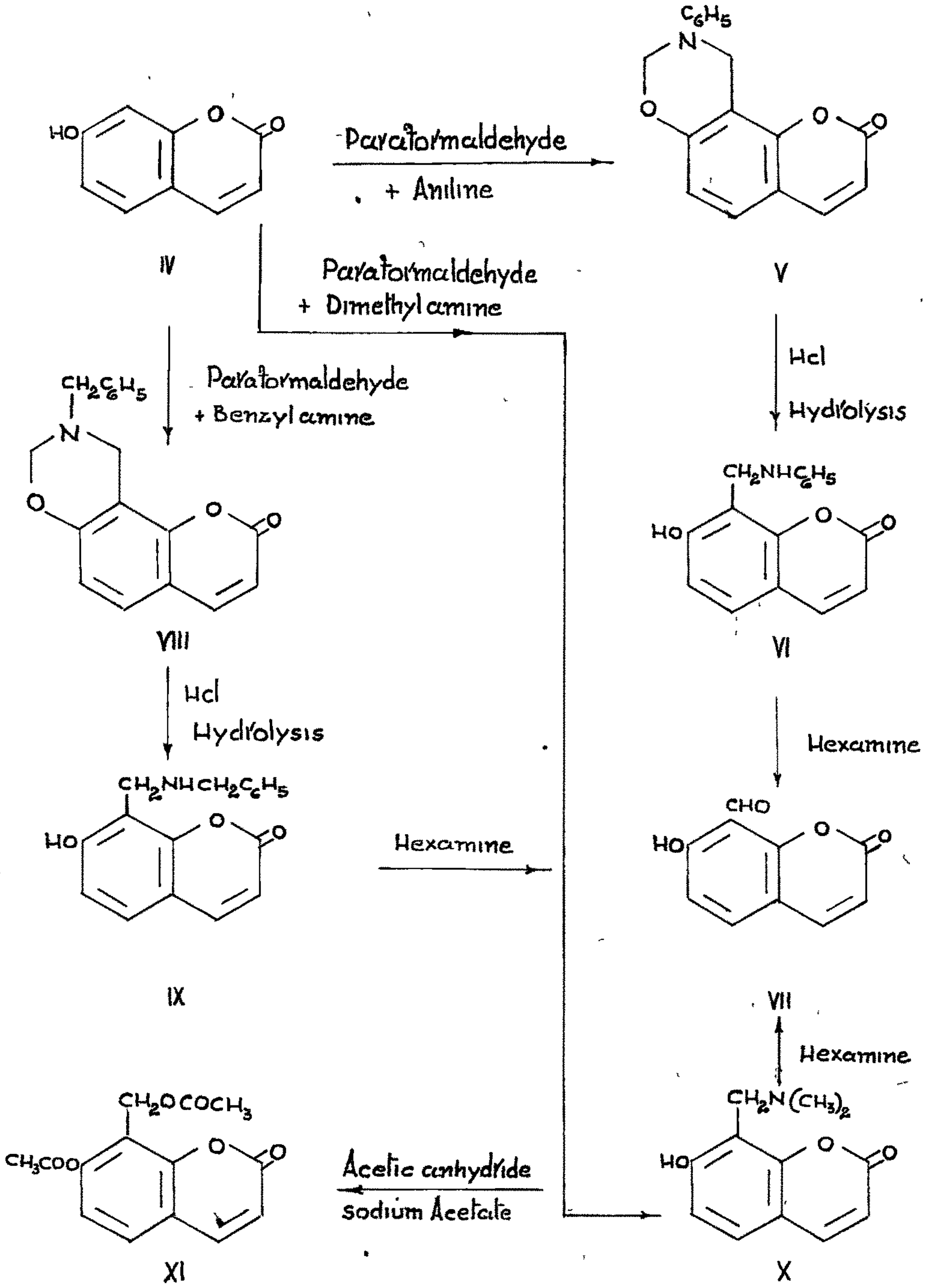
7-Hydroxycoumarin (IV) when treated with formaldehyde and aniline in equimolecular proportions gave a product to which 7-hydroxy-8-anilinomethylcoumarin (VI) structure has been assigned as on treatment with hexamethylene tetramine it gave 7-hydroxy-8-formylcoumarin (VII). With double the molecular proportion of formaldehyde a product insoluble in alkali was obtained to which 2'H-3'-phenyl-3'-4'-dihydro-1',3'-oxazino-5',6',8,7-coumarin (V) structure has been assigned. This on hydrolysis with hydrochloric acid gave the 8-anilinomethylcoumarin (VI) described above.

<u>Mannich reaction on 6-hydroxycoumarin</u>(chart on p.153)

6-Hydroxycoumarin (XII) on treatment with formaldehyde and dimethylamine in equimolecular quantities gave 6-hydroxy-5-dimethylaminomethylcoumarin (XIII). On treatment with hexamethylene tetramine it furnished the known 6-hydroxy-5-formylcoumarin (XVII),(Naik and Thakor, (J. Org. Chem., 1957, <u>22</u>, 1626) as seen by direct comparison. On treatment with acetic anhydride in presence of sodium acetate it yielded 6-acetoxy-5-acetoxymethylcoumarin (XIV).

6-Hydroxycoumarin (XII) when treated with formaldehyde and benzylamine in equimolecular quantities gave a product insoluble in alkali to which 2'H-3'-benzyl-3',4'-

dihydro-1',3'-oxazino-5',6',5,6-coumarin (XIX) structure has been assigned. This on hydrolysis with hydrochloric acid gave 6-hydroxy-5-benzylaminomethylcoumarin (XVIII) which on treatment with hexamethylenetetramine yielded the known 6-hydroxy-5-formylcoumarin (XVII).



With double the molecular quantity of paraformaldehyde 6-hydroxycoumarin yielded 2'H-3'-benzyl-3',4'-dihydro-1',3'-oxazino-5',6',5,6-coumarin in better yield.

6-Hydroxycoumarin (XII) when treated with formaldehyde and aniline in equimolecular proportions yielded 2'H-3'-phenyl-3',4'-dihydro-1',3'-oxazino-5',6',5,6-coumarin (XV) in poor yield.

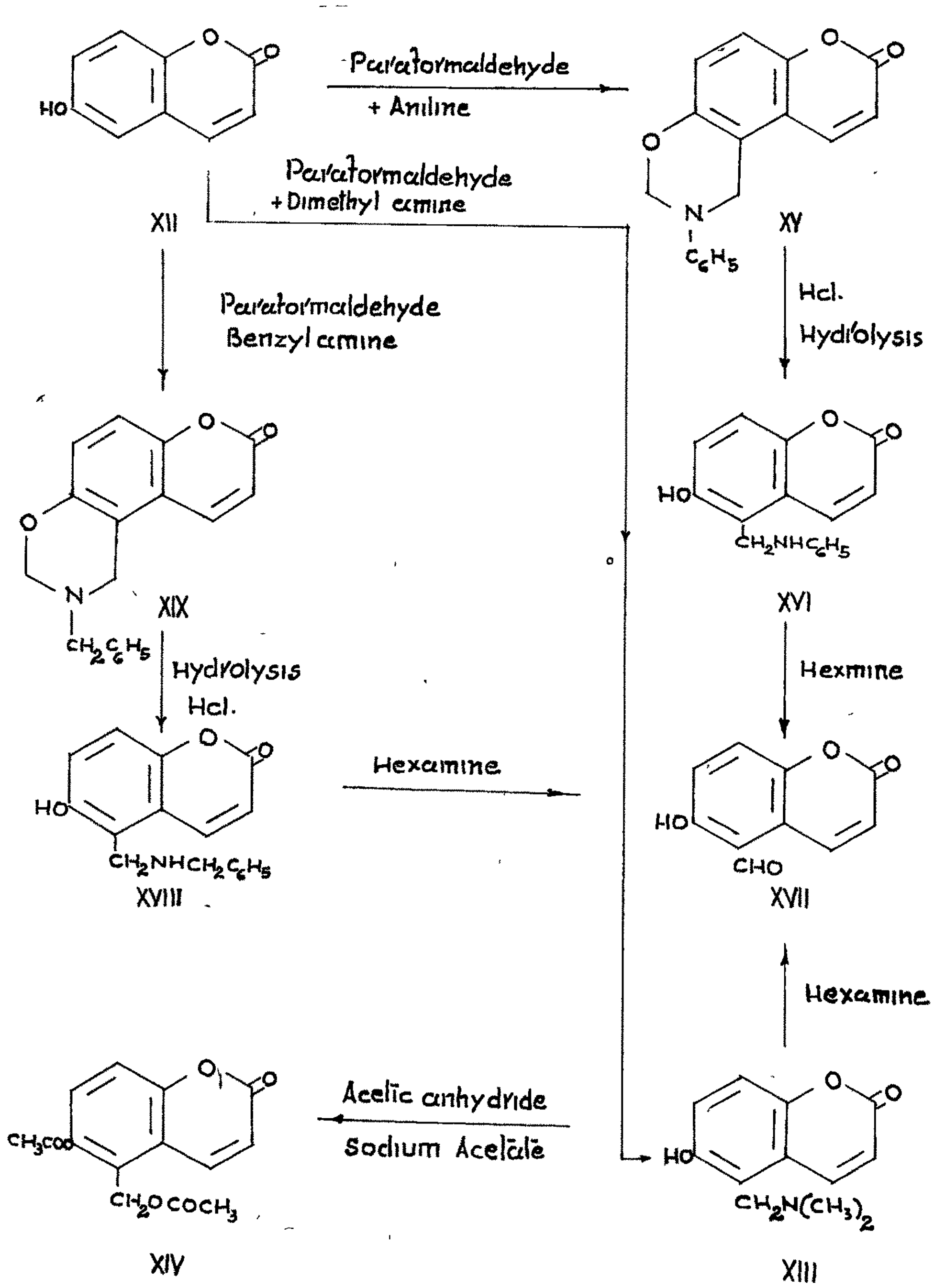
This on treatment with alcoholic con. hydrochloric acid gave 6-hydroxy-5-anilinomethylcoumarin (XVI) which on treatment with hexamethylene tetramine furnished the known 6-hydroxy-5-formylcoumarin (XVII). Better yields of (XV) were obtained when twice the molecular proportion of formaldehyde was taken.

(chart on p.155)

Mannich reaction on Ethyl 7-hydroxycoumarin-3-carboxylate

Ethyl 7-hydroxycoumarin-3-carboxylate (XX) when condensed with formalin and dimethylamine in equimolecular proportions gave a good yield of a mono aminomethylcoumarin derivative. This product has been assigned the 8-dimethylaminomethylcoumarin structure for the following reasons :

The Mannich reaction product could be either the 6 or the 8-dialkylaminomethyl derivative. The dialkylaminomethylcoumarin was brominated when a monobromo derivative was obtained which could be either the 6-bromo or the 8-bromo derivative depending on the position of the alkyl aminomethyl group. When ethyl 7-hydroxy-6-bromocoumarin-3-carboxylate was subjected to Mannich reaction with formalin and dimethylamine it gave a product identical. with the above bromo derivative of the dialkylaminomethylcoumarin which proves that the dialkylamino methyl group must be in the 8-position.



Ethyl 7-hydroxycoumarin-3-carboxylate (XX) on condensation with formalin and benzylamino in molar ratio of 1 : 2 : 1 yielded a product which was insoluble in alkali to which the structure 2'H-3'-benzyl-3',4'-dihydro-3-carbethoxy-1',3'-oxazino-5',6',8,7-coumarin (XXV) has been assigned. As on bromination it yielded a bromo derivative identical with the one synthesised from ethyl 7-hydroxy-6-bromocoumarin-3-carboxylate through Mannich reaction with formalin and benzylamine. The bromo derivative is therefore 2'H-3'-benzyl-3',4'-dihydro-3-carbethoxy-6-bromo-1',3'-oxazino-5',6',8,7-coumarin (XXIV).

Ethyl 7-hydroxycoumarin-3-carboxylate (XX) on condensation with formalin and aniline gave a 1,3-oxazine derivative to which in ~~an~~ analogy with the previous work the structure 2'H-3'-phenyl-3',4'-dihydro-3-carbethoxy-1',3'-oxazino-5',6',8,7-coumarin (XXVI) has been assigned. On bromination it did not give a crystallisable product. Ethyl 7-hydroxy-6-bromocoumarin-3-carboxylate on condensation with formalin and aniline under varying conditions also did not give any crystallisable product. Unworkable paste was obtained.

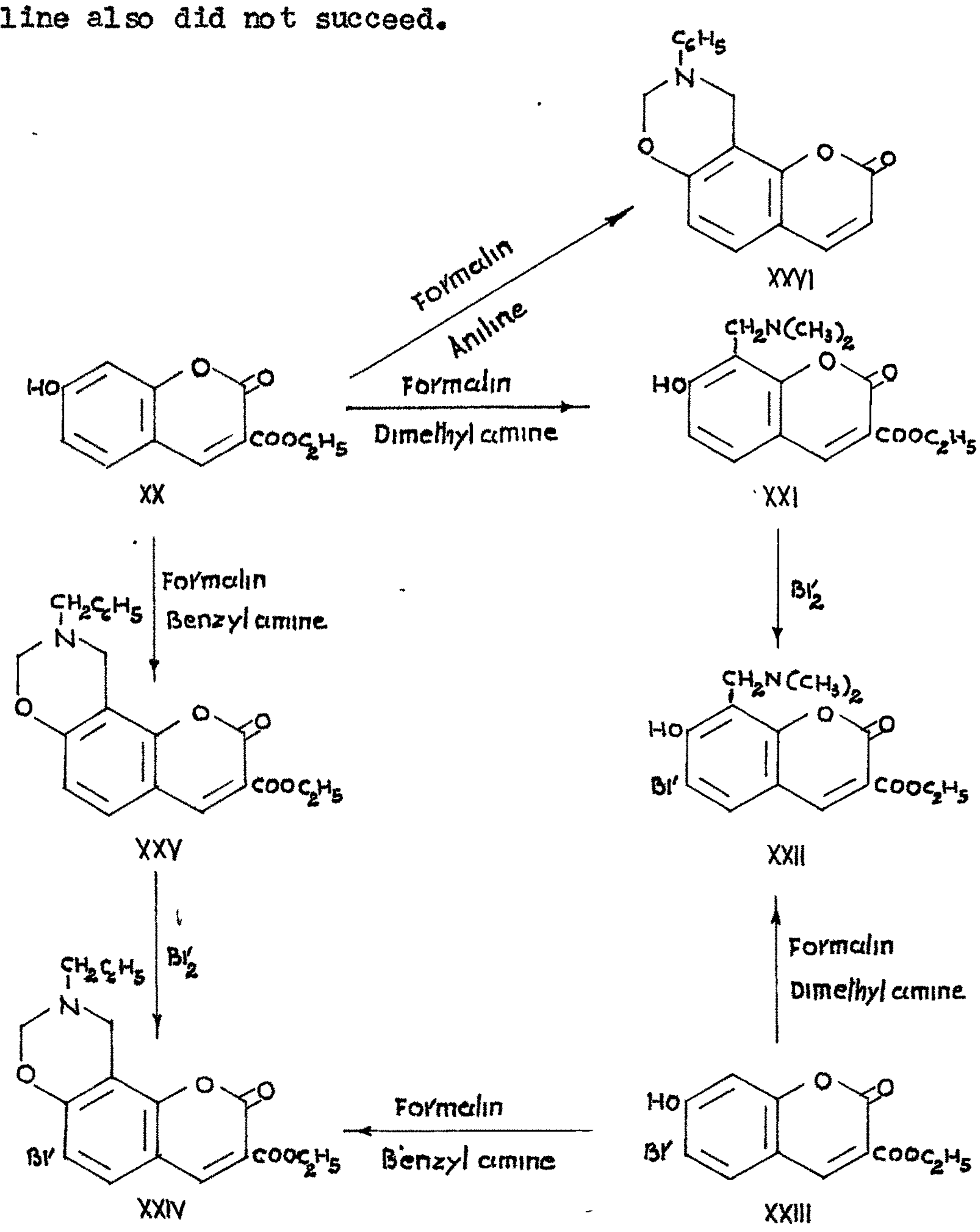
Other attempted Mannich reactions

Condensation of simple coumarin with formalin or paraformaldehyde and benzylamine or dimethylamine did not succeed. Only original coumarin was recovered unchanged.

7-Methoxycoumarin also did not condense with formalin or paraformaldehyde and dimethylamine or benzylamine under varying conditions. Only the original coumarin was recovered unchanged.

Mannich reaction on methyl 7-hydroxycoumarin-6-carboxylate either with formalin or paraformaldehyde and dimethylamine or benzylamine under different experimental condition did not succeed. Only the original coumarin was recovered unchanged.

Mannich reaction on ethyl 7-hydroxy-8-bromocoumarin 3-carboxylate with formalin and dimethylamine or benzylamine or aniline also did not succeed.



EXPERIMENTAL

Mannich reaction on 7-hydroxycoumarin with paraformaldehyde and dimethylamine : 7-Hydroxy-8-dimethylaminomethylcoumarin hydrochloride

Paraformaldehyde (0.3 g. ; 0.01 mole) was dissolved in absolute alcohol (5 ml. containing 0.1 g. of potassium hydroxide) by gentle heating. Dimethylamine (1 ml. of 37 % aqueous solution ; 0.01 mole) was added gradually with cooling. 7-Hydroxycoumarin (1.62 g. ; 0.01 mole) and absolute alcohol (5 ml.) were then successively added to the reaction mixture and it was then gently refluxed on a steam-bath for 2 hours. It was kept at room temperature over-night. Next day dry hydrogen chloride gas was passed into the solution and it was chilled below 0°. The product which separated was filtered and washed with little ether. It crystallised from alcohol-ether mixture in needles, m.p. 223-224°. Yield 1.6 g. It was insoluble in ether, benzene, chloroform but easily soluble in alcohol, acetone and water. Its aqueous solution showed brilliant blue fluorescence.

Analysis :

4.862 mg. of the substance gave 10.02 mg. of carbon dioxide and 2.384 mg. of water.

7.922 mg. of the same substance gave 0.382 ml. of nitrogen at 31° and 746 mm.

9.862 mg. of the same substance gave 5.432 mg. of silver chloride.

Found : C=56.24 % ; H=5.48 % ; N=5.31 % ; Cl=13.63

$C_{12}H_{13}O_3N.HCl$ requires : C=56.36 % ; H=5.48 % ; N=5.48 % ; Cl=13.9

7-Acetoxy-8-acetoxymethylcoumarin

The above hydrochloride (0.5 g.) was heated with acetic anhydride (5 ml.) and fused sodium acetate (1 g.) on a steam bath for 2 hours. The product obtained on adding the reaction mixture to cold water and keeping over-night crystallised from benzene-petroleum ether mixture in needles, m.p. 123-124°.

Analysis :

4.510 mg. of the substance gave 10.10 mg. of carbon dioxide and 1.800 mg. of water.

Found : C = 61.11 % ; H = 4.46 %.

$C_{14}H_{12}O_6$ requires : C = 60.87 % ; H = 4.38 %.

Sommelet reaction on 7-hydroxy-8-dimethylaminomethylcoumarin hydrochloride

The above hydrochloride (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, m.p. 189°. Yield 0.2 g. Mixed m.p. with an authentic specimen prepared according to Spath et al. (Ber., 1935, 68B, 940) was not depressed.

Mannich reaction on 7-hydroxycoumarin with paraformaldehyde and benzylamine : 7-Hydroxy-8-benzylaminomethylcoumarin

Paraformaldehyde (0.3 g. ; 0.01 mole) was dissolved in absolute alcohol (5 ml. containing 0.1 g. of potassium hydroxide) by gentle warming. Benzylamine (1.1 ml.; 0.01 mole) and absolute alcohol (5 ml.) were then successively added to the reaction mixture. 7-Hydroxycoumarin (1.62 g. ; 0.01 mole) was added and the reaction mixture gently refluxed on a steam bath for 2 hours and left over-night. Next day the alcohol was removed and the paste obtained was triturated with petroleum ether (b.p. 40-60°) and then extracted with benzene. The residue obtained after removal of benzene on repeated crystallisation from benzene-petroleum ether gave needles, m.p. 130-132°. Yield 10 %. The substance was easily soluble in benzene, chloroform, acetone, alcohol and dioxan. When the reaction time was shortened or if the reaction was carried out by keeping at room temperature for 24 hours the original coumarin was recovered.

Analysis :

4.390 mg. of the substance gave 11.638 mg. of carbon dioxide and 2.064 mg. of water.

9.928 mg. of the same substance gave 0.444 ml. of nitrogen at 30° and 748 mm.

Found : C = 72.35 % ; H = 5.26 % ; N = 4.95 %.

$C_{17}H_{15}O_3N$ requires : C = 72.58 % ; H = 5.37 % ; N = 4.98 %.

2'H-3'-benzyl-3',4'-dihydro-1',3'-oxazino-5',6', 8,7-coumarin

~~The~~ Another product in the above reaction was obtained when the mother liquor from the above reaction mixture was evaporated, ~~and~~ This was repeatedly crystallised from benzene-petroleum ether in needles, m.p. 125-126°. Yield 0.4 g. The compound was soluble in hydrochloric acid and insoluble in alkali. This compound was obtained in better yield when the quantity of paraformaldehyde was doubled.

Analysis :

4.502 mg. of the substance gave 12.156 mg. of carbon dioxide and 2.128 mg. of water.

8.792 mg. of the same substance gave 0.356 ml. of nitrogen at 30° and 748 mm.

Found : C = 73.68 % ; H = 5.30 % ; N = 4.49 %.

$C_{18}H_{15}O_3N$ requires : C = 73.70 % ; H = 5.15 % ; N = 4.78 %.

7-Hydroxy-8-benzylaminomethylcoumarin

A mixture of the above oxazino-coumarin derivative (1.5 g. ; 0.005 mole) in absolute alcohol (10 ml.) and concentrated hydrochloric acid (5 ml.) 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 after a solid began to separate out in the distilling flask. Ethyl alcohol was added to effect the solution of the precipitated solid and the solution was neutralised by addition of just sufficient solid sodium bicarbonate solution. The solid thus precipitated was washed with water dried then crystallised from benzene-petroleum ether in needles, m.p. 130-132°. Yield 0.8 g. Mixed m.p. with 7-hydroxy-8-benzylaminomethylcoumarin described above was not depressed.

Treatment of a portion of the distillate with 2,4-dinitrophenylhydrazine 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-dinitrophenylhydrazone of formaldehyde was not depressed.

7-Acetoxy-8-(N-acetyl) benzylaminomethylcoumarin

7-Hydroxy-8-benzylaminomethylcoumarin (0.5 g.) was heated with acetic anhydride (5 ml.) 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 benzene-petroleum ether in needles, m.p. 137-138°.

Analysis :

4.616 mg. of the substance gave 11.644 mg. of carbon dioxide and 2.198 mg. of water.

8.444 mg. of the same substance gave 0.297 ml. of nitrogen at 30° and 748 mm.

Found : C = 68.84 % ; H = 5.33 % ; N = 3.90 %.

$C_{21}H_{19}O_5N$ requires : C = 69.03 % ; H = 5.24 % ; N = 3.83 %.

Sommelet reaction on 7-hydroxy-8-benzylaminomethyl coumarin

7-Hydroxy-8-benzylaminomethylcoumarin (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-hydroxy-8-formylcoumarin described before.

Mannich reaction on 7-hydroxycoumarin with paraformaldehyde and aniline : 7-Hydroxy-8-anilinomethyl coumarin

Paraformaldehyde (0.3 g. ; 0.01 mole) was dissolved in absolute alcohol (5 ml. containing 0.1 g. of potassium hydroxide) by gentle warming. Aniline (0.93 ml. ; 0.01 mole) and absolute alcohol (5 ml.) were then successively added to the reaction mixture. 7-Hydroxycoumarin (1.62 g. ; 0.01 mole) was added and the reaction mixture gently refluxed on a steam bath for 2 hours and left over-night. Next day the alcohol was removed and the paste obtained was triturated with petroleum ether (b.p. 40-60°) and then extracted with benzene. The residue obtained after removal of benzene on repeated crystallisations from dilute alcohol gave ~~in~~ needles, m.p. 168-170°. Yield 0.7 g.

Analysis :

4.208 mg. of the substance gave 11.168 mg. of carbon dioxide and 1.902 mg. of water.

7.646 mg. of the same substance gave 0.352 ml. of nitrogen at 29° and 748 mm.

Found : C = 72.43 % ; H = 5.06 % ; N = 5.12 %.
$C_{16}H_{13}O_3N$ requires : C = 71.91 % ; H = 4.87 % ; N = 5.24 %.

2'H-3'-phenyl-3',4'-dihydro-1',3'-oxazino-5',6', 8,7-coumarin

~~The~~ Another product in the above reaction was obtained when the mother liquor from the above reaction mixture was evaporated and ~~this~~ the product repeatedly crystallised from benzene-petroleum ether in needles, m.p. 138-140°. Yield < 10 %. The compound was soluble in hydrochloric acid and insoluble in alkali. It was soluble in benzene, chloroform , acetone and alcohol. This compound was obtained in better yield when the quantity of paraformaldehyde was doubled.

Analysis :

4.474 mg. of the substance gave 12.026 mg. of carbon dioxide and 1.988 mg. of water.

10.91 mg. of the same substance gave 0.494 ml. of nitrogen at 40° and 753 mm.

Found : C = 73.35 % ; H = 4.97 % ; N = 4.89 %.

$C_{17}H_{13}O_3N$ requires : C = 73.11 % ; H = 4.69 % ; N = 5.02 %.

7-Hydroxy-8-anilinomethylcoumarin

To the above ~~coumarino-m-oxazine~~ derivative (1.5 g. ; 0.005 mole) was added absolute alcohol (10 ml.) and concentrated 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 after a solid began to separate out in the distilling flask. Alcohol was added to effect the solution of the solid and the solution was neutralised by addition of just sufficient saturated solution of sodium bicarbonate. The solid thus precipitated was washed with water and crystallised from dilute alcohol in needles, m.p. 168-170°. Yield 0.7 g. Mixed m.p. with 7-hydroxy-8-anilinomethylcoumarin described above was not depressed.

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

Sommelet reaction on 7-hydroxy-8-anilinomethyl coumarin

7-Hydroxy-8-anilinomethylcoumarin (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 working as before gave a product m.p. and mixed m.p. of which with 7-hydroxy-8-formylcoumarin was 189°.

Mannich reaction on 6-hydroxycoumarin with paraformaldehyde and dimethylamine : 6-Hydroxy-5-dimethylaminomethylcoumarin

Paraformaldehyde (0.3 g. ; 0.01 mole) was dissolved in warm absolute alcohol (5 ml. containing 0.1 g. of potassium hydroxide) and dimethylamine (1 ml. ; 37 % aqueous solution ; 0.01 mole) was added gradually with external cooling. 6-Hydroxycoumarin (1.62 g. ; 0.01 mole) in absolute alcohol (5 ml.) was then added. The reaction mixture was then gently refluxed on a steam bath for 2 hours and then left over-night at room temperature. Next day the solvent was completely removed and the residue was extracted with chloroform. The product obtained after removal of chloroform crystallised from benzene-petroleum ether mixture in ~~fine~~ needles, m.p. 105-106°. Yield 0.8 g.

Analysis :

4.430 mg. of the substance gave 10.700 mg. of carbon dioxide and 2.464 mg. of water.

9.082 mg. of the same substance gave 0.506 ml. of nitrogen at 28° and 748 mm.

Found : C = 65.91 % ; H = 6.22 % ; N = 6.21 %.

$C_{12}H_{13}O_3N$ requires : C = 65.74 % ; H = 5.98 % ; N = 6.39 %.

6-Hydroxy-5-dimethylaminomethylcoumarin hydrochloride

This was obtained in good yield when the above reaction mixture after keeping for 24 hours at room temperature was saturated with dry hydrogen chloride gas. It was chilled below 0° and the product which separated crystallised from alcohol-ether mixture in needles, m.p. 235-236°. Yield 1.2 g.

Analysis :

4.162 mg. of the substance gave 8.572 mg. of carbon dioxide and 1.966 mg. of water.

14.420 mg. of the same substance gave 7.966 mg. of silver chloride.

Found : C = 56.21 % ; H = 5.29 % ; Cl = 13.66 %.

$C_{12}H_{13}O_3N.HCl$ requires : C = 56.36 % ; H = 5.48 % ; Cl = 13.91 %.

Sommelet reaction on 6-hydroxy-5-dimethylaminomethylcoumarin hydrochloride

6-Hydroxy-5-dimethylaminomethylcoumarin hydrochloride (1 g.) was refluxed with acetic acid (15 ml.) and hexamethylene tetramine (1 g.) for 4 hours on a wire gauze. Concentrated hydrochloric acid (10 ml.) was added and the mixture was refluxed further for 1 hour. The product obtained on working up the reaction mixture as usual crystallised from benzene in needles, m.p. 189°. Yield 0.2 g. Mixed melting point with an authentic specimen of 6-hydroxy-5-formylcoumarin prepared according to Naik and Thakor (J. Org. Chem., 1957, 22, 1626) from 6-hydroxycoumarin was not depressed.

6-Acetoxy-5-acetoxymethylcoumarin

6-Hydroxy-5-dimethylaminomethylcoumarin hydrochloride (0.5 g.) was heated with acetic anhydride (5 ml.) and fused sodium acetate (1 g.) on a water bath for 2 hours. The product obtained on working up the reaction mixture as usual crystallised from petroleum ether in needles, m.p. 117-118°.

Analysis :

4.856 mg. of the substance gave 10.84 mg. of carbon dioxide and 2.040 mg. of water.

Found : C = 60.92 % ; H = 4.70 %.
$C_{14}H_{12}O_6$ requires : C = 60.87 % ; H = 4.38 %.

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

Paraformaldehyde (0.6 g. ; 0.02 mole) was dissolved in absolute alcohol (5 ml. containing 0.1 g. of potassium hydroxide) by gentle warming. Benzylamine (1.1 ml. ; 0.01 mole) was added gradually with cooling followed by 6-hydroxycoumarin (1.62 g. ; 0.01 mole) 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 yellow needles separated. The product collected after keeping the reaction mixture at room temperature over-night crystallised from benzene in needles, m.p. 145-146°. Yield 1.8 g. It was soluble in concentrated hydrochloric acid and insoluble in sodium hydroxide. It was also soluble in alcohol, acetone, chloroform and benzene. No 6-hydroxy-5-benzylamino-methylcoumarin was obtained in the above reaction and also when one mole of paraformaldehyde was used.

Analysis :

4.424 mg. of the substance gave 11.914 mg. of carbon dioxide and 2.056 mg. of water.

10.49 mg. of the same substance gave 0.484 ml. of nitrogen at 39° and 753 mm.

	Found	: C = 73.49 % ; H = 5.19 % ; N = 5.0 %.
$C_{18}H_{15}O_3N$	requires	: C = 73.70 % ; H = 5.15 % ; N = 4.78%.

6-Hydroxy-5-benzylaminomethylcoumarin

The above ~~coumarino-~~ oxazine (1.4 g. ; 0.005 mole) 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. 132°. Yield 0.6 g. Treatment of a portion of the distillate with 2,4-dinitrophenylhydrazine hydrochloride gave the 2,4-dinitrophenyl hydrazone of formaldehyde.

Analysis :

4.36 mg. of the substance gave 11.638 mg. of carbon dioxide and 2.10 mg. of water.

8.592 mg. of the same substance gave 0.377 ml. of nitrogen at 30° and 750 mm.

Found : C = 72.84 % ; H = 5.39 % ; N = 4.88 %.

$C_{17}H_{15}O_3N$ requires : C = 72.58 % ; H = 5.37 % ; N = 4.98 %.

6-Hydroxy-5-benzylaminomethylcoumarin hydrochloride

The above hydrochloride was obtained when 6-hydroxy-5-benzylaminomethylcoumarin (0.2 g.) was dissolved in alcohol and treated with hydrogen chloride. The product obtained on cooling and diluting the reaction mixture with ether was recrystallised from alcohol-ether mixture in needles, m.p. 229°.

Analysis :

4.522 mg. of the substance gave 10.634 mg. of carbon dioxide and 1.936 mg. of water.

11.374 mg. of the substance gave 5.082 mg. of silver chloride.

Found : C = 64.18 % ; H = 4.80 % ; Cl = 11.06 %.

$C_{17}H_{15}O_3N.HCl$ requires : C = 64.24 % ; H = 5.03 % ; Cl = 11.18 %.

Sommelet reaction on 6-hydroxy-5-benzylaminomethylcoumarin

6-Hydroxy-5-benzylaminomethylcoumarin (1 g.) was refluxed with acetic acid (15 ml.) and hexamethylene tetramine (1 g.) for 4 hours. The reaction mixture on working up as before gave 6-hydroxy-5-formylcoumarin. The mixed melting point with an authentic specimen synthesised as mentioned earlier was not depressed.

Mannich reaction on 6-hydroxycoumarin with paraformaldehyde and aniline : 2'H-3'-phenyl-3',4'-dihydro-1',3'-oxazino-5',6',5,6-coumarin

Paraformaldehyde (0.6 g. ; 0.02 mole) was dissolved in absolute alcohol (5 ml. containing 0.1 gm. of potassium hydroxide) by gentle warimg and aniline (0.93 ml. ; 0.01 mole) was added gradually with cooling.

~~and~~ 6-Hydroxycoumarin (1.62 g. ; 0.01 mole) was then added and the reaction mixture gently refluxed on a steam bath for 2 hours. The product which separated on keeping the reaction mixture over-night crystallised from benzene-petroleum ether mixture in needles, m.p. 193-195°. Yield 1.4 g. It was insoluble in alkali and soluble in hydrochloric acid.

<u>Analysis</u> :

4.34 mg. of the substance gave 11.650 mg. of carbon dioxide and 1.650 mg. of water.

8.332 mg. of the same substance gave 0.375 ml. of nitrogen at 31° and 748 mm.

Found : C = 73.25 % ; H = 4.25 % ; N = 4.97 %.

$C_{18}H_{15}O_3N$ requires : C = 73.10 % ; H = 4.69 % ; N = 5.02 %.

6-Hydroxy-5-anilinomethylcoumarin

The above oxazinocoumarin derivative (1.4 g. ; 0.005 mole) and ethyl alcohol (10 ml.) and concentrated hydrochloric acid (5 ml.) were heated on a wire gauze in a distilling flask and the distillate collected in water (25 ml.). More dilute alcohol (20 ml. ; 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 addition of more ethanol and the solution was neutralised with just sufficient sodium bicarbonate solution. The yellow solid obtained crystallised from dilute alcohol, m.p. 198-200°. Yield 0.7 g.

Analysis :

4.232 mg. of the substance gave 11.176 mg. of carbon dioxide and 1.852 mg. of water.

8.922 mg. of the same substance gave 0.418 ml. of nitrogen at 30° and 750 mm.

Found : C = 72.07 % ; H = 4.90 % ; N = 5.20 %.
$C_{16}H_{13}O_3N$ requires : C = 71.91 % ; H = 4.87 % ; N = 5.24 %.

Sommelet reaction on 6-hydroxy-5-anilinomethylcoumarin

6-Hydroxy-5-anilinomethylcoumarin (1 g.) was refluxed with acetic acid (15 ml.) and hexamethylene tetramine (1 g.) for 4 hours. The reaction mixture on working up as before gave 6-hydroxy-5-formylcoumarin as seen by direct comparison with an authentic specimen synthesised as mentioned earlier.

Mannich reaction on ethyl 7-hydroxycoumarin-3-carboxylate with formalin and dimethylamine : Ethyl 7-hydroxy-8-dimethylaminomethylcoumarin-3-carboxylate

To formalin (2 ml. ; 0.02 mole) in absolute ethanol (10 ml.), dimethylamine (1 ml. ; 0.01 mole) was added followed by ethyl 7-hydroxycoumarin-3-carboxylate (2.3 g. ; 0.01 mole) 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. 182°. Yield 1.2 g.

Analysis :

4.228 mg. of the substance gave 9.580 mg. of carbon dioxide and 2.334 mg. of water.

6.142 mg. of the same substance gave 0.257 ml. of nitrogen at 36° and 754 mm.

Found : C = 61.83 % ; H = 6.18 % ; N = 4.59 %.

$C_{15}H_{17}O_5N$ requires : C = 61.85 % ; H = 5.88 % ; N = 4.81 %.

Ethyl 7-hydroxy-6-bromo-8-dimethylaminomethylcoumarin-3-carboxylate

The above coumarin ester (0.3 g. ; 0.001 mole) and sodium acetate (1 g.) were dissolved in acetic acid (2 ml.) and bromine (0.16 g. ; in acetic acid (0.001 mole) was added drop-wise with stirring. The reaction mixture was then added to water and the product obtained crystallised from benzene-petroleum ether in needles, m.p. 218°. Mixed m.p. with ethyl 7-hydroxy-8-dimethylaminomethyl-6-bromo-coumarin-3-carboxylate prepared by the mannich reaction on ethyl 7-hydroxy-6-bromocoumarin-3-carboxylate with formalin and dimethylamine described below was not depressed.

Formalin (1 ml. ; 0.01 mole) was added to absolute ethanol (5 ml.) followed by dimethylamine (0.5 ml. ; 0.005 mole). Ethyl 7-hydroxy-6-bromocoumarin-3-carboxylate (1.6 g. ; 0.005 mole) and absolute alcohol (5 ml.) were then added and the reaction mixture was gently refluxed on a steam bath for 2 hours. The solid which separated on keeping the reaction mixture over-night at room temperature crystallised from benzene-petroleum ether mixture in needles, m.p. 218°. Yield 0.8 g.

Analysis :

8.122 mg. of the substance gave 0.278 ml. of nitrogen at 28° and 746 mm.

10.490 mg. of the same substance gave 5.298 mg. of silver bromide.

Found : N = 3.81 % ; Br = 21.49 %.

$C_{15}H_{15}O_5\overset{N}{\wedge}Br$ requires : N = 3.80 % ; Br = 21.68 %.

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

To formalin (2 ml. ; 0.02 mole) in absolute ethanol (10 ml.), benzylamine (1.1 ml. ; 0.01 mole) was added gradually followed by ethyl 7-hydroxycoumarin-3-carboxylate (2.3 g. ; 0.01 mole) and absolute alcohol (5 ml.). The reaction mixture was gently refluxed on a steam bath for 2 hours and left at room temperature. The separated needles were recrystallised from benzene-petroleum ether, m.p. 148-150°. Yield 2.1 g.

Analysis :

4.612 mg. of the substance gave 11.718 mg. of carbon dioxide and 2.260 mg. of water.

9.992 mg. of the same substance gave 0.315 ml. of nitrogen at 29° and 750 mm.

Found : C = 69.34 % ; H = 5.48 % ; N = 3.51 %.

$C_{21}H_{19}O_5N$ requires : C = 69.03 % ; H = 5.24 % ; N = 3.83 %.

2'H-3'-benzyl-3',4'-dihydro-3-carboethoxy-6-bromo-1',3'-oxazino-5',6',8,7-coumarin

The above coumarin ester (0.36 g. ; 0.001 mole) and sodium acetate (1 g.) were dissolved in acetic acid (3 ml.) and bromine (0.16 g.) in acetic acid (0.001 mole) added gradually with stirring. The product, which separated almost immediately, crystallised from benzene-petroleum ether in needles, m.p. 195°. Mixed melting point with 2'H,3'-benzyl-3',4'-dihydro-3-carboethoxy-6-bromo-1',3'-oxazino-5',6',8,7-coumarin prepared by the Mannich reaction on ethyl 7-hydroxy-6-bromocoumarin-3-carboxylate with formalin and benzylamine as under was not depressed.

Formalin (1 ml. ; 0.01 mole) was added to absolute alcohol (5 ml.) followed by benzylamine (0.5 ml. ; 0.005 mole). Ethyl 7-hydroxy-6-bromocoumarin-3-carboxylate (1.6 g. ; 0.005 mole) and absolute alcohol (5 ml.) were then added and the reaction mixture gently refluxed on a steam-bath for 2 hours. It was kept at room temperature over-night. The separated solid crystallised from benzene-petroleum ether mixture in needles, m.p. 195°. Yield 1 g. The substance was soluble in benzene, acetone, alcohol and chloroform. It was soluble in concentrated hydrochloric acid and insoluble in sodium hydroxide solution.

Analysis :

8.922 mg. of the substance gave 0.256 ml.of nitrogen at 28° and 746 mm.

11.214 mg. of the same substance gave 4.722 mg. of silver bromide.

Found :- N = 3.20 % ; Br = 17.92 %.

$C_{21}H_{18}O_5NBr$ requires : N = 3.15 % ; Br = 18.02 %.

Mannich reaction on ethyl 7-hydroxycoumarin-3-carboxylate with formalin and aniline : 2'H-3'-phenyl-3',4'-dihydro-3-carboethoxy-1',3'-oxazino-5',6',8,7-coumarin

To formalin (2 ml. ; 0.02 mole) in absolute ethanol (10 ml.) aniline (0.93 ml. ; 0.01 mole) was added followed by ethyl 7-hydroxycoumarin-3-carboxylate (2.3 g. ; 0.01 mole) and absolute alcohol (5 ml.). The reaction mixture was gently refluxed on a steam bath for 2 hours and then left over-night. The separated solid crystallised from benzene-petroleum ether in needles, m.p. 168-170°. Yield 1.8 g.

Analysis :

4.792 mg. of the substance gave 12.052 mg. of carbon dioxide and 2.178 mg. of water.

9.47 mg. of the same substance gave 0.376 ml. of nitrogen at 40° and 753 mm.

Found : C = 68.63 % ; H = 5.08 % ; N = 4.29 %.

$C_{20}H_{17}O_5N$ requires : C = 68.37 % ; H = 4.88 % ; N = 3.99 %.

Attempted bromination of 2'H,3'-phenyl-3',4'-dihydro-3-carboethoxy-1',3'-oxazino-5',6',8,7-coumarin

The above coumarin ester (0.3 g. ; 0.001 mole) and sodium acetate (1 g.) were dissolved in acetic acid (2 ml.) and bromine (0.16 g.) in acetic acid (0.001 mole) was added drop-wise with stirring. The solid obtained on adding the reaction mixture to water did not crystallise to give a pure product~~s~~.

Attempted Mannich reaction on ethyl 7-hydroxy-6-bromocoumarin-3-carboxylate with formalin and aniline

Formalin (1 ml. ; 0.01 mole) was added to absolute alcohol (5 ml.) followed by aniline (0.5 ml. ; 0.05 mole), ethyl 7-hydroxy-6-bromocoumarin-3-carboxylate (1.5 g. ; 0.05 mole) and absolute alcohol (5 ml.). The reaction mixture was gently refluxed on a steam-bath for 2 hours and then kept at room temperature over-night. Next day the solvent was removed. ~~and~~ The paste obtained could not be crystallised through any solvent.

Attempted Mannich reaction on 7-methoxycoumarin with paraformaldehyde and dimethylamine

Paraformaldehyde (0.3 g. ; 0.01 mole) was dissolved in absolute alcohol (5 ml. containing 0.1 g. of potassium hydroxide) by gentle warming and dimethylamine (1 ml. ; 0.01 mole) was added gradually with cooling. 7-Methoxycoumarin (1.76 g. ; 0.01 mole) and absolute alcohol (5 ml.) were then added to the reaction mixture and it was then gently refluxed on a steam bath for 2 hours. On working up the reaction mixture as usual only the original 7-methoxycoumarin was recovered. Increase in the heating time from 2 to 16 hours did not give any mannich base. Reactions with benzylamine and aniline also did not succeed.

Attempted ~~m~~Mannich reaction on methyl 7-hydroxycoumarin-6-carboxylate with formalin and dimethylamine

Formalin (1 ml. ; 0.01 mole) was dissolved in absolute alcohol (5 ml.) and dimethylamine (1 ml. ; 0.01 mole) was added gradually with cooling. Methyl-7-hydroxycoumarin-~~3~~6-carboxylate (2.2 g. ; 0.01 mole) and absolute alcohol (5 ml.) were then added and the reaction mixture was gently refluxed on a steam bath for 2 hours. The product which separated on keeping the reaction mixture at room temperature over-night was the original coumarin. Increase in the duration of heating of the reaction mixture also gave the same results.

Attempted ~~m~~Mannich reaction on ethyl 7-hydroxy-8-bromocoumarin-3-carboxylate with formalin and dimethylamine

Formalin (2 ml. ; 0.02 mole) was dissolved in absolute alcohol (5 ml.) and dimethylamine (1 ml. ; 0.01 mole) was added gradually. Ethyl 7-hydroxy-8-bromocoumarin-3-carboxylate (1.5 g. ; 0.05 mole) and absolute alcohol (6 ml.) were then added and the reaction mixture was gently refluxed on a steam bath for 2 hours. A paste was obtained on removal of the solvent from which no pure product could be obtained by treatment with various solvents. Reactions with benzylamine and formalin also did not succeed.