GENERAL METHODS OF SYNTHESIS
OF 4-HYDROXYCOUMARIN
Since the work presented in this thesis relates to the synthesis of 4-hydroxy-l-thiacoumarins and related compounds (the sulphur analogues of 4-hydroxycoumarins) as possible anticoagulants, a brief account of the methods available for the synthesis of the latter is given in the following pages.

(a) **From acetyl salicyloyl chloride and sodiomalonate ester: (Anschutz's method)**\(^1\).

Acetyl salicyloyl chloride condenses with acetocetic or malonic ester to give 3-carbethoxy-4-hydroxycoumarin. This on hydrolysis and decarboxylation gives 4-hydroxycoumarin.
(b) **By cyclisation of acetyl methyl salicylates in the presence of alkali metal.**

A simpler method but one resulting in a poorer yield (21\%) is the method due to Pauly and Lockemann.\(^2\) This consists in the treatment of acetyl methyl salicylate with metallic sodium in an inert solvent.

\[ \text{Phloroglucinol} \quad \text{condenses with malononitrile under} \]

(c) **Condensation of ethyl cyano acetate with phenols. (Hoesch method)\(^3\).**

Phloroglucinol condenses with malononitrile under
the conditions of Hoesch to yield \( \omega \)-cyanoacetyl phloroglucinol and 2,4,6-2',4',6'-hexahydroxydibenzoylmethane. \( \omega \)-Cyanoacetyl phloroglucinol is converted into 4,5,7-trihydroxycoumarin by boiling with dilute acids.

Resorcinol in the same way yields 6-cyanoacetyl-resorcinol, hydrolysed to 4,7-dihydroxycoumarin.

Instead of malononitrile cyanoacetic acid may be employed in this synthesis.

(d) Condensation of \( \alpha \)-hydroxyacetophenone with ethylcarbonate.

Boyd and Robertson have shown that \( \alpha \)-hydroxyacetophenones and their \( \omega \)-substituted derivatives, which
are conveniently accessible, readily undergo condensation with ethylcarbonate containing 1-2% alcohol, in the presence of sodium to give 4-hydroxycoumarins. The method is convenient and is of wide applicability. The scope of the reaction is illustrated by the following application to a variety of ketones.

(e) Cyclisation of diarylmalonates in the presence of anhydrous aluminium chloride (Ziegler's method)\(^5\).

Ziegler and Junek developed a convenient method for the synthesis of 4-hydroxycoumarins viz., condensation of the appropriate phenol with malonic acid in the presence of phosphorus oxychloride and subsequent
cyclisation of the intermediate diaryl malonic ester thus formed with anhydrous aluminium chloride.

It may be pointed out that the conversion of diaryl malonic ester into the corresponding 4-hydroxy-coumarin may involve the elimination of a molecule of phenol and the formation of intermediate ketene ester.

(f) Cyclisation by using zinc chloride and phosphorus oxychloride.

Shah et al. have evolved a synthesis of 4-hydroxy coumarins in which phenol is treated with equimolecular proportion of malonic acid in the presence of a mixture of anhydrous zinc chloride and phosphorus oxychloride as the condensing agent at temperatures preferably between 60-75°. The success of this reaction is dependent upon the specific condensing action of the mixture of anhydrous zinc chloride and phosphorus oxychloride, which are individually almost ineffective. Other condensing agents such as anhydrous aluminium chloride, stannic chloride and ferric chloride are also effective. Lower alkyl esters of malonic acid or substituted malonic acid may also be used in this reaction but usually poor yields of 4-hydroxycoumarins are then obtained.

Small quantities of diaryl malonates were often
isolated from the reaction product. The possibility of formation of diarylmalonates in situ and their further cyclisation under the conditions of this method was however, unlikely since no appreciable quantity of 4-hydroxy-coumarins could be obtained when diaryl malonates such as diphenyl malonate were heated with a mixture of anhydrous zinc chloride and phosphorus oxychloride under the usual conditions of this method.

This method has been successfully employed for the condensation of malonic acid with various phenols like, phenol, o-, m- and p-cresols, α- and β-naphthols, and resorcinol to yield the corresponding known 4-hydroxy-coumarins. They have also condensed substituted malonic acids, such as α-propyl-, α-butyl-, and phenyl malonic acids with phenol to give corresponding known 3-substituted-4-hydroxycoumarins.

(g) By thermal condensation.

Lefeuvre and Mentzer⁸ synthesised 4-hydroxy-coumarins by thermal condensation of phenol with
thiophenyl malonic ester at 150-60° in an atmosphere of nitrogen to give 3-thiophenyl-4-hydroxycoumarin. This when refluxed in excess of water (pH 5) in the presence of Raney nickel afforded 4-hydroxycoumarin.

\[
\begin{align*}
\text{OH} & + \text{PHS NC} \xrightarrow{N_2} \text{COOCH}_3 \\
\text{H} & \text{O} \\
\text{O} & \text{H} \\
\text{SPh} & \xrightarrow{N_2} \text{COOCH}_3 \\
\end{align*}
\]

Similarly by this method they have prepared 4,7-dihydroxycoumarin and 4-hydroxy-7-methylcoumarin.

Thermal condensation of substituted malonic esters with phenol leads to 4-hydroxycoumarins carrying substituents in the 3-position. The yields increase with the increase of molecular weight of the malonic ester. By heating methylmalonic ester with 1 mole of phenol for 48 hours at 200-40°, 3-methyl-4-hydroxycoumarin is obtained.

\[
\begin{align*}
\text{OH} & + \text{HC NC} \xrightarrow{N_2} \text{COOCH}_3 \\
\text{H} & \text{O} \\
\text{O} & \text{H} \\
\text{CH}_3 & \\
\end{align*}
\]

By this method they have prepared 3-propyl-, 3-phenyl-4-hydroxycoumarins in 15%, 20% yields respectively.
GENERAL METHODS OF SYNTHESIS
OF 4-HYDROXY-1-THIACOUMARINS
Though a large number of 4-hydroxycoumarins substituted in the benzene ring or pyrone ring of the 4-hydroxycoumarin molecule (by any one of the methods described in previous pages) have been reported in the literature, similar attempts on the synthesis of the various sulphur analogues viz., 4-hydroxy-1-thiacoumarins are lacking. The one case so far reported in the literature relates to the synthesis of the simplest member viz., 4-hydroxy-1-thiacoumarin.

The following which are an adaptation of the methods discussed under the coumarins are (a) Mentzer's method, (b) Ziegler's method, (c) Shah's method and (d) Mentzer's thermal method.
(a) **Mentzer's method.**

This involves the condensation of acetylthiosalicylic acid with sodiummalonic ester.

\[
\begin{align*}
\text{Ph-S-CH_3} + \text{NaHCCOOCH_3} & \rightarrow \\
\text{Ph-S-CH_3} + \text{NaHCCOOCH_3} & \rightarrow \\
\end{align*}
\]

(b) **Ziegler's method.**

Ziegler and Junek have reported that simple 4-hydroxy-1-thiacoumarin is formed by the condensation of thiophenol with malonic acid in the presence of phosphorus trioxide.

\[
\begin{align*}
\text{Ph-SH} + \text{HC(OH)COOH} + \text{POCl}_3 & \rightarrow \\
\text{Ph-SH} + \text{HC(OH)COOH} + \text{POCl}_3 & \rightarrow \\
\end{align*}
\]
oxychloride and subsequent cyclisation of the diphenyl dithiomalonate thus formed by anhydrous aluminium chloride.

(c) Shah's method.⁶

Shah et al. have effected a synthesis of 4-hydroxy-1-thiacoumarin using thiophenol and malonic acid as the reactants by employing a mixture of zinc chloride and phosphorus oxychloride as the condensing agent at a temperature range of 60-75°.

(d) Mentzer's thermal method.¹²

Thiophenol when treated with α-naphthyl substituted diethyl malonate at 320-30° in an atmosphere of nitrogen and inert solvent yields the 3-α-naphthyl-substituted-4-hydroxy-1-thiacoumarin.
REFERENCES

1. Anschütz, Ber., 36, 468 (1903).
2. Pauly and Lockemann, Ber., 48, 28 (1915).
3. Sonn, Ber., 50, 1292 (1917).
PRESENT WORK
The need for the study of sulphur analogues of the particularly potent anticoagulants like dicoumarol, warfarin, coumechlor etc., has been stressed in the introductory section. Hence the synthesis of such compounds has been now carried out. Further, since very few of the sulphur analogues of 4-hydroxycoumarins have been so far synthesised, a comprehensive scheme of synthesis of these compounds has been undertaken and the results recorded.

The different methods available for the synthesis of 4-hydroxy-1-thiacoumarin have been recorded in the previous pages. Amongst these methods the method due to Ziegler and Junek\textsuperscript{1} was found to be convenient and adopted
in the present work. This method involves the condensation of appropriate thiophenol with malonic acid in the presence of phosphorus oxychloride and subsequent cyclisation of dithiophenylmalonic ester thus formed by anhydrous aluminium chloride. Since an alkyl or halogen atom is known to have beneficial activity on these compounds, the synthesis of such compounds has been attempted in the first instance.

A large number of thiophenols (I) carrying alkyl or halogen substituents in the free benzenoid nucleus have been condensed with malonic or α-alkyl substituted malonic acids (II) in the presence of phosphorus oxychloride to give dithiophenylmalonic esters (III), which when heated with anhydrous aluminium chloride yield the desired 4-hydroxy-1-thiacoumarins (VI). It may be pointed out that the conversion of dithiophenylmalonic ester into the corresponding 4-hydroxy-1-thiacoumarin may involve the elimination of a molecule of thiophenol and the formation of an intermediate ketene ester (V) as shown below. Possible formation of such ketene esters during the synthesis of 4-hydroxycoumarins has been substantiated by Ziegler and Junek.1
The following starting materials were required to prepare the above 4-hydroxy-1-thiacoumarins.

**Thiophenols.**

Two alternative methods have been employed for the preparation of thiophenols, viz.,

(a) Starting with appropriate amine and adopting the Leuckart method

(b) Starting with appropriate hydrocarbon converting into the sulphonyl derivative and reducing it with zinc and sulphuric acid to the corresponding thiophenol.
The following thiophenols have been prepared by Leuckart method:

Thiophenol, \( \sigma^- \), \( \pi^- \), and \( \rho^- \)-thiocresol, \( \sigma^- \), \( \pi^- \), and \( \rho^- \)-chlorothiophenol, \( \sigma^- \) and \( \rho^- \)-bromothiophenol, 2-methyl-4-bromothiophenol, 2-bromo-4-methylthiophenol, 2-chloro-4-methylthiophenol, 2-methyl-4-chlorothiophenol and 2,5-dimethylthiophenol.

Method (a) which has been used to a large extent in the course of the present work involves:

(i) preparation of the corresponding diazonium salts
(ii) coupling of the diazonium salts with excess of potassium ethyl xanthate at 70-80\(^\circ\)
(iii) hydrolysis of the resulting xanthates with alkali
(iv) isolation of the thiophenols.

The course of the reaction is as follows:

\[
\begin{align*}
\text{Ar.NH}_2 \quad \text{aq. HCl, NaN_2} & \quad \xrightarrow{\text{\L}} \quad \text{Ar.N = N Cl} \quad \xrightarrow{\text{K.S.C. OEt}} \\
\text{Ar.N = N.S.C.OEt} \quad \xrightarrow{70-80\^\circ} & \quad \text{Ar.S.C.OEt} \\
\text{\textcolor{red}{\text{alc. KOH}}} & \quad \text{Ar.SK} \quad \text{\textcolor{red}{\text{Acid}}} \quad \xrightarrow{\text{}} \quad \text{Ar.SH}
\end{align*}
\]
(b) Sulphonyl chloride method involves:

(i) preparation of aryl sulphonyl chlorides and

(ii) reduction of sulphonyl chlorides to mercaptans.

A very satisfactory method consists in the interaction of aromatic hydrocarbons with excess of chlorosulphonic acid in presence of solvents like chloroform or carbon tetrachloride.

\[
\text{Ar.H} + \text{Cl.SO}_2\text{OH} \rightarrow \text{Ar.SO}_2\text{OH} + \text{HCl}
\]

\[
\text{Ar.SO}_2\text{OH} + \text{Cl.SO}_2\text{OH} \rightarrow \text{Ar.SO}_2\text{Cl} + \text{H}_2\text{SO}_4
\]

These sulphonyl chlorides have been reduced to the corresponding thiophenols by the action of zinc and sulphuric acid.

\[
\text{Ar.SO}_2\text{Cl} + \text{Zn} + \text{H}_2\text{SO}_4 \rightarrow \text{Ar.SH}
\]

2,5-Dichloro-, and 3,4-dichlorothiophenols have been prepared by sulphonyl chloride method.

The various anilines required for the preparation of above thiophenols were prepared by the following sequence of reactions:
α-Alkyl substituted malonic acids:

The α-alkyl substituted malonic acids required as starting materials were prepared by conventional methods described in the literature.

α-Methyl-, and α-ethyl malonic acids were obtained by treating the malonic ester with methyliodide and ethyliodide in sodium ethoxide to get α-methyl or α-ethyl malonic esters. The corresponding acids were obtained by hydrolysing the above esters with potassium hydroxide solution.

\[
\begin{align*}
\text{CH}_2\text{COOCH}_3 + \text{CH}_3\text{I} \rightleftharpoons \text{CH}_2\text{COOCH}_3\text{CH}_3
\end{align*}
\]

\[
\begin{align*}
\text{CH}_2\text{COOCH}_3 + \text{C}_2\text{H}_5\text{I} \rightleftharpoons \text{CH}_2\text{COOC}_2\text{H}_5
\end{align*}
\]

\[
\begin{align*}
\text{CH}_2\text{COOCH}_3\text{CH}_3 + \text{KOH} \rightarrow \text{CH}_2\text{COOH} + \text{CH}_3\text{COOH}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_2\text{COOCH}_3\text{C}_2\text{H}_5 + \text{KOH} \rightarrow \text{CH}_2\text{COOH} + \text{C}_2\text{H}_5\text{COOH}
\end{align*}
\]

R = Methyl, ethyl, n-propyl or n-butyl

n-Propyl-, and n-butyl malonic acids were obtained by treating the malonic ester with n-propyl bromide and n-butyl bromide to get the corresponding α-substituted esters. Hydrolysis of the above esters by potassium hydroxide solution afforded the desired α-substituted malonic acids.
Chart I.

<table>
<thead>
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<th>Chart I.</th>
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<tr>
<td>Chart I.</td>
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<tr>
<td><img src="chart.png" alt="Diagram" /></td>
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<td>(Cv1)</td>
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<tr>
<td>a) $R = R_1 = R_3 = H$ a) $R_4 = CH_3$</td>
</tr>
<tr>
<td>b) $R_2 = CH_3$ b) $R_2 = Cl, R_4 = CH_3$</td>
</tr>
<tr>
<td>c) $R = CH_3$ c) $R_4 = C_2H_5$</td>
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<tr>
<td>d) $R_2 = Cl$ d) $R_2 = Br, R_4 = C_2H_5$</td>
</tr>
<tr>
<td>e) $R_1 = Cl$ e) $R = CH_3, R_4 = C_2H_5$</td>
</tr>
<tr>
<td>f) $R = Cl$ f) $R_1 = R_2 = Cl, R_4 = C_2H_5$</td>
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<tr>
<td>g) $R_2 = Br$ g) $R = CH_3, R_2 = Cl, R_4 = C_2H_5$</td>
</tr>
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<td>h) $R = Br$ h) $R_4 = n-C_3H_7$</td>
</tr>
<tr>
<td>i) $R_1 = R_2 = Cl$ i) $R_2 = Cl, R_4 = n-C_3H_7$</td>
</tr>
<tr>
<td>j) $R = R_3 = Cl$ j) $R = CH_3, R_4 = n-C_3H_7$</td>
</tr>
<tr>
<td>k) $R = R_2 = CH_3$ k) $R = Br, R_2 = CH_3, R_4 = n-C_3H_7$</td>
</tr>
<tr>
<td>l) $R = R_3 = CH_3$ l) $R_4 = n-C_4H_9$</td>
</tr>
<tr>
<td>m) $R = CH_3, R_3 = Cl$ m) $R_1 = CH_3, R_4 = n-C_4H_9$</td>
</tr>
<tr>
<td>n) $R = CH_3, R_2 = Br$ n) $R = R_3 = CH_3, R_4 = n-C_4H_9$</td>
</tr>
<tr>
<td>o) $R = Cl, R_2 = CH_3$</td>
</tr>
</tbody>
</table>

(Undesigned 'R' groups refer to hydrogen)
Elucidation of the structure of 4-hydroxy-1-thiacoumarins viz., whether they exist as the \( \alpha \)-pyrone, \( \gamma \)-pyrone or 2,4-diketo form is of great theoretical significance. Hence a study of the infrared data of 4-hydroxy-1-thiacoumarins and of their products of methylation is undertaken. A number of 4-hydroxy-1-thiacoumarins (VI) carrying alkyl or halogen substituents in the benzene nucleus, have been methylated by using dimethyl sulphate as the methylating agent to obtain 4-methoxy-1-thiacoumarins (VIa).

\[
\begin{align*}
\text{a)} & \quad R = \text{CH}_3, \quad R' = \text{H} \\
\text{b)} & \quad R = \text{CH}_3, \quad R' = \text{CH}_3 \\
\text{c)} & \quad R = \text{CH}_3, \quad R' = \text{Cl} \\
\text{d)} & \quad R = \text{CH}_3, \quad R' = \text{Br}
\end{align*}
\]
Among the simple derivatives of 4-hydroxy-coumarin of great interest may be mentioned dicoumarol, which has been shown to be the agent responsible for the hemorrhagic "sweet clover disease" of cattle, and which has been easily prepared by condensing formaldehyde with two molecules of 4-hydroxycoumarin. In the following pages an account of the synthesis of sulphur analogues of dicoumarol is presented. Simple and various benz-substituted (halogen, methyl) 4-hydroxy-1-thiacoumarins (VI) have been condensed with formaldehyde to give the corresponding bis-4-hydroxy-1-thiacoumarins (VIII), probably involving the formation of 3-alkylidene-2,4-diketo-thiachroman (VII) as shown below.

![Chemical Structures](image-url)
Extension of the work employing the various aromatic aldehydes (IX) viz., the isomeric tolualdehydes, halogenobenzaldehydes etc., in place of formaldehyde has led to the synthesis of various 3,3'-arylidenebis-(4-hydroxy-1-thiacoumarins) (X).

With salicylaldehyde (XI) as the aldehyde component in such condensations, two different products were
obtained depending upon the molar ratio of 4-hydroxy-1-thiacoumarin (VI) to salicylaldehyde. With equimolar proportions an yellow compound probably having the structure (XIII) 3-(a-hydroxybenzal)-2,4-diketo-1-thiachroman was obtained. When the molar ratio of 4-hydroxy-1-thiacoumarin to salicylaldehyde was two to one and the time of heating increased a colourless product which is assigned the structure (XV) 3-(6-oxo-(1)-benzothiapyran-4,3-b)-(1)-benzopyran-7-yl-7-4-hydroxy-1-thiacoumarin was obtained. The course of the reaction may be indicated as involving viz.,

(1) an aldol condensation of salicylaldehyde with 4-hydroxy-1-thiacoumarin to give the intermediate transitory hydroxy compound (XII)

(2) a Michael reaction between the compound (XIII) and a second molecule of 4-hydroxy-1-thiacoumarin (VI) to give the intermediate (XIV) which eliminates a molecule of water to give (XV) involving the enolic hydroxyl of one of the 4-hydroxy-1-thiacoumarins and the phenolic hydroxyl of the o-hydroxy-benzylidene residue. All these are in agreement with the observations of Link et al., relating to the behaviour of simple 4-hydroxycoumarin, under similar conditions.
The above compound (XV) has been characterised by acetylation with acetic anhydride and pyridine to give the monoacetate (XVI). It may be pointed out that the mixture of compounds (XIII) and (XV) normally formed by refluxing salicylaldehyde with excess of 4-hydroxy-1-thiacoumarin for a long time can be separated by taking advantage of ready solubility of the diketothiachroman in ethanol.

With a view to verify whether the anticoagulant activity of these 4-hydroxy-1-thiacoumarins is dependent on the presence of a hydroxyl group in the 4-position, the various arylidenebis-(4-hydroxy-1-thiacoumarins) (X) obtained above, have been dehydrated to yield the corresponding epoxy compounds. Such a dehydration has been effected either by acetic anhydride and pyridine or by acetyl chloride in pyridine to give 3,3'-arylidene-4,4'-epoxydithiacoumarins (XVII).
In the previous pages has been recorded the result of the reaction between 4-hydroxy-l-thiacoumarin and formaldehyde. This involves an aldol type of condensation between two molecules of 4-hydroxy-l-thiacoumarin and one molecule of formaldehyde and illustrates a case of nucleophilic substitution at the active methylene carbon atom in the 3-position. A logical extension of such reaction will be a study of the Mannich reaction between such active methylene compounds like 4-hydroxy-l-
thiacoumarin (VI), formaldehyde and various aliphatic primary and secondary amines. Such a study has now been carried out and the results recorded. The products of this reaction have been the 3-aminomethyl derivatives (XVIII).

Since the reaction between 4-hydroxy-1-thiacoumarin and formaldehyde to give the 3,3'-methylenebis-

\[
\begin{align*}
\text{(vi)} & \quad \text{amine} \quad \text{HCHO} \\
\text{(XVIII)} & 
\end{align*}
\]

\((4\text{-hydroxy-1-thiacoumarin})\) (VIIIa) is a very rapid one, the order in which the reactants are added to make the Mannich reaction possible is important. This is achieved by adding a solution of 4-hydroxy-1-thiacoumarin (0.01 mole) in absolute ethanol to a solution of the amine (0.0125 mole) and formaldehyde (0.01 mole, 35 %) in absolute ethanol at room temperature. Further it has been found that the ease with which the Mannich reaction proceeds with the various amines differ greatly depending on
the nature of the amine employed. The reaction proceeds very fast in the case of primary amines while it is relatively slow when secondary amines are employed. Thus, while in the former case the reaction could proceed at room temperature, in the latter case the reactants had to be mixed at the boiling point and subsequently allowed to stand for a number of hours.

It is well known that many of the products obtained in the Mannich reaction, especially those derived from secondary amines undergo decomposition into the amine and unsaturated compound. The intermediate formation of such compounds has also been postulated by Robertson and Link to explain the quantitative formation of 3,3'-methylenebis-(4-hydroxycoumarin) (XXII), when the Mannich reaction product (XIX) of 4-hydroxycoumarin with piperidine is heated in an aqueous acid solution at 100°C. It was suggested by these authors that the Mannich base decomposes to an unsaturated compound (3-methylidene-2,4-diketocchroman) (XX), which in turn undergoes reverse aldol reaction to give 4-hydroxycoumarin (XXI). Subsequently interaction of one molecule of the former (XX) with one molecule of the latter compound (XXI) gives 3,3'-methylenebis-(4-hydroxycoumarin) (XXII). The course of the reaction may probably be represented as shown below:
It has now been found that the Mannich reaction product obtained employing 4-hydroxy-1-thiacoumarin, formaldehyde and piperidine behaves in a similar manner, when heated in aqueous acid solution.
The significance of 4-hydroxy-l-thiacoumarin and related compounds viz., carrying alkyl or aminomethyl substituents in the 3-position has been indicated in the earlier pages. 3-Acyl-4-hydroxycoumarin, a compound containing tricarbonyl methane (XXV) has been found to
possess remarkable activity against several bacteria.\textsuperscript{10}

The 3-acyl compounds which may be regarded as derivatives of 4-hydroxycoumarin with monocarboxylic acids show bactericidal and anticoagulant activity\textsuperscript{11} and therefore interest in these substances has increased recently. The known methods of preparing 3-acyl-4-hydroxycoumarin involve,

(1) condensation of suitable derivatives of salicylic acid with \(\beta\)-ketoester\textsuperscript{12},

(2) heating 4-hydroxycoumarin with acetyl chloride and sodium in toluene to give only 5\% yield of the desired product. However, smooth reaction occurred when pyridine was used as solvent and 3-acyl-4-hydroxycoumarins were obtained in better yields,\textsuperscript{13}

(3) submitting the 4-acetoxycoumarin to Fries migration with anhydrous aluminium chloride, various authors\textsuperscript{14,15} prepared 3-acyl-4-hydroxycoumarins. But these methods are rather complicated and the yields are not satisfactory. Hence, Klosa\textsuperscript{16} introduced a new and much simpler method for the preparation of 3-acyl-4-hydroxycoumarins by treating 4-hydroxycoumarin with aliphatic carboxylic acids in the presence of phosphorus oxychloride. This reaction can be carried out conveniently with good yields and hence, this
method has been now adopted during the course of the present work for the condensation of 4-hydroxy-1-thiacoumarins (VI) with aliphatic carboxylic acids (XXIII) to obtain 3-acyl-4-hydroxy-1-thiacoumarins (XXIV). These 3-acyl compounds gave a positive ferric chloride test in alcoholic solution.

However, the structures of these compounds have been established by independent synthesis as in a typical case viz., acetylation of 4-hydroxy-1-thiacoumarin (VI) to 4-acetoxy derivative (XXVI) and its conversion to 3-acetyl-4-hydroxy-1-thiacoumarin (XXVII) by Fries migration.

Further 4-acetoxy derivative has been condensed with acetic acid in presence of phosphorus oxychloride to give 3-acetyl-4-acetoxy-1-thiacoumarin (XXVIII).
In analogy with the acyl compounds which have been shown to be active, it was felt that the 3-formyl-4-hydroxycoumarins may have desirable anticoagulant activity. Hence the synthesis of 3-formyl-4-hydroxy-1-thiacoumarins has been undertaken.
A large number of hydroxy coumarins have been successfully formylated by the method of Duff\textsuperscript{17} employing hexamine as a formylating agent. However, it has been found by Ziegler and Maier\textsuperscript{18} not useful for the formylation of 4-hydroxycoumarin. By employing N-methylformanilide and phosphorus oxychloride as formylating agent, they have been able to get 3-formyl-4-hydroxycoumarin in 18% yield.

Similarly in the course of the present work it has been found that the 4-hydroxy-1-thiacoumarin when heated with hexamine in acetic acid does not yield 3-formyl 4-hydroxy-1-thiacoumarin. However, the following modification has been found helpful. It has been found earlier that 4-hydroxy-1-thiacoumarin undergoes Mannich reaction readily with various primary and secondary amines to give Mannich bases in good yields. In the case, when piperidine was employed the Mannich base was obtained in 80% yield. Hence 3-piperidinomethyl-4-hydroxy-1-thiacoumarin (XXIX) was allowed to interact with hexamine in acetic acid medium to give 3-formyl-4-hydroxy-1-thiacoumarin (XXX) in 30% yield.
3-Formyl-4-hydroxy-1-thiacoumarin has been characterised by the preparation of 2,4-dinitrophenylhydrazone. It also forms anil (XXXI) with o-phenylenediamine.

![Chemical structure](attachment:image.png)

(XXXI)

Alternate method to introduce a formyl group in 4-hydroxy-1-thiacoumarin has been tried. Thus, 4-hydroxy-1-thiacoumarin has been treated with N-methylformanilide and phosphorus oxychloride but the starting material was always recovered.

Advantage has been taken of the o-hydroxy-aldehyde group in the above 3-formyl-4-hydroxy-1-thiacoumarin to form the α-pyrone ring expecting such compounds to possess anticoagulant activity. Two alternative routes have been adopted to prepare such compounds during the present work.

1. **Perkin's method**: 3-Formyl-4-hydroxy-1-thiacoumarin is submitted to Perkin's reaction giving rise to α-pyrano (5',6',3,4)-1-thiacoumarin (XXXII).

2. **Knovenagel's reaction**: 3-Formyl-4-hydroxy-1-thiacoumarin has been condensed with diethylmalonate in
presence of piperidine to give \( \alpha\)-pyrano-4'-carbethoxy-
\( (5',6'-3,4)\)-1-thiacoumarin (XXXIII).

\( \alpha\)-Pyrano-4'-methyl-(5',6'-3,4)-1-thiacoumarin
(XXXIV) has been obtained by the condensation of 4-hydroxy-
1-thiacoumarin with ethylacetoacetate in presence of
anhydrous aluminium chloride. It may be pointed out that
Patel and Usgaonkar\(^{20}\) have found anhydrous aluminium
chloride as a convenient agent in such a condensation.
Shortly after the anticoagulant 3,3'-methylenebis-(4-hydroxycoumarin), (Dicoumarol), was isolated from sweet clover hay, identified and synthesised its marked toxicity in the rat was noted. Later O'Connor reported the successful use of dicoumarol as a rodenticide and made a comprehensive study of related compounds. He was able to show that 3-(α-phenyl-β-acetylethyl)-4-hydroxycoumarin (warfarin) is approximately fifty times more lethal and in addition, the time to effect death is about half that required by dicoumarol.

In the earlier work it was observed that when salicylaldehyde is condensed with 4-hydroxy-1-thiacoumarin, an α,β-unsaturated ketone is first formed which reacts with another molecule of 4-hydroxy-1-thiacoumarin by Michael addition. Warfarin is the product of such a Michael addition between α,β-unsaturated ketone like benzoal acetone and 4-hydroxycoumarin. Now the condensation of 4-hydroxy-1-thiacoumarin (VI) with benzoal acetone (XXXV), p-chlorobenzoal acetone and anisal acetone has been carried out to get the sulphur analogues of warfarin (XXXVI), coumechlor etc.
The Michael condensation is usually carried out in an alcoholic medium in the presence of an acid or base catalyst. According to Conner and McClellen, secondary amines (e.g. piperidine) are the most suitable catalyst in that they seldom cause other than the normal condensation, but they are not as effective as metallic alkoxides. Valuable observation made by Link et al. is that the condensation of benzal acetone with 4-hydroxy-coumarin under the usual conditions with piperidine as catalyst gives a mixture of normal condensation product and cyclic ketal formed by reaction with ethanol. However, these authors could overcome the difficulty by carrying out the Michael condensation using dioxan as medium and piperidine as catalyst and could obtain the desired product in quantitative yield.

Now sulphur analogues of well-known anticoagulants like warfarin, coumechlor etc., have been synthesised through the Michael condensation discussed above. Thus,
substituted 4-hydroxy-1-thiacoumarins have been condensed with substituted benzal acetones employing piperidine as catalyst to give sulphur analogues of warfarin, coumechlor etc. in satisfactory yields.

**Substituted benzal acetones:**

Benzal-, p-chlorobenzal- and p-methoxybenzal acetones required for the Michael condensation were prepared by the Claisen-Schmidtt condensation employing the appropriate aldehyde and acetone in the presence of aqueous alkali.

**Chart VI.**

\[ \text{(xxxvi)} \]

\[
\begin{align*}
\text{a) } & \quad R = H; \ R' = H \\
\text{b) } & \quad R = \text{Cl}; \ R' = H \\
\text{c) } & \quad R = \text{Br}; \ R' = H \\
\text{d) } & \quad R = H; \ R' = \text{Cl} \\
\text{e) } & \quad R = \text{Cl}; \ R' = \text{Cl} \\
\text{f) } & \quad R = \text{Br}; \ R' = \text{Cl} \\
\text{g) } & \quad R = H; \ R' = \text{OCH}_3 \\
\text{h) } & \quad R = \text{Br}; \ R' = \text{OCH}_3
\end{align*}
\]
REFERENCES


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