CHAPTER V

CHLOROMETHYLATION OF COUMARINS

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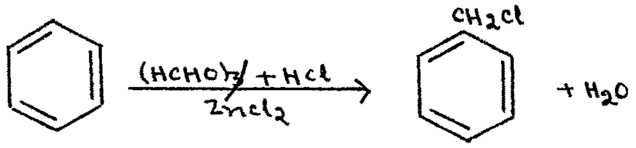
The replacement of a hydrogen atom by a chloromethyl group in a single operation has come to be known as chloromethylation. A chloromethylated product usually results when the condensation of formaldehyde with aromatic compounds is carried out in presence of hydrogen chloride.



A survey of the chloromethylation of aromatic compounds has been made by Fuson and McKeever (Organic Reactions Vol 1 ; John Wiley and Sons, New York, 1942, p. 63)

Chloromethylation is of much value in ~~the~~ synthetic work inasmuch as the chloromethyl group is reactive and the chlorine atom can be replaced by other groups. Alcohols result when such compounds are hydrolysed by heating with water either alone or under pressure. Alcohols can be prepared indirectly through the saponification of acetic acid esters obtained from interaction of chloromethylated compound with acetic acid in presence of fused sodium acetate. Many alcohols with various functional groups have been prepared by this method. Chloromethyl group can be converted to cyanomethyl group which in its turn would give on saponification acetic acid derivatives. On reduction it can be converted to methyl group.

Aldehydes are obtained by the interaction of halomethyl compounds with hexamine (Sommelet reaction).

$$R\,CH_2Cl + (\,CH_2\,)_6\,N_4 \longrightarrow R\,CH_2\,(CH_2)_6\,N_4Cl$$
$$\xrightarrow{H_2O} R\,CHO + HCl + (CH_2)_6\,N_4$$

On condensation with secondary amines such as diethylamine or dimethylamine the chloromethyl derivatives give various dialkylaminomethyl derivatives which are substances of therapautic value.

Application of the reaction :

Aromatic hydrocarbons such as benzene, naphthalene, anthracene, phenanthracene, biphenyl and many of their derivatives have been chloromethylated. The introduction of an alkyl group in the benzene nucleus enhances the reactivity of the hydrocarbon, highly alkylated homologues reacting rapidly in the absence of catalyst. Nauta and Dienske (Rec. trav. Chim., 1936, 55, 1000 ; C.A.,1937, 31, 1776) chloromethylated mesityleme without using any catalyst and obtained the mono as well as the dichloromethyl derivatives. Braun and Nells (Ber., 1934, 67, 1094) chloromethylated m-xylene and obtained the dichloromethyl derivative. Chloromethyl group preferentially enters the para position with respect to an alkyl group but a small amount of the ortho chloromethylated isomer is also formed. A second chloromethyl group usually can be introduced and sometimes excellent yields of the dichloromethyl derivative are obtained.

Halogens and nitro group in the aromatic ring retard the reaction. Stephen et al. (J. Chem. Soc., 1920, 117, 510) found that nitrobenzene and ortho and p-nitrotoluene give chloromethyl derivatives but in low yield. Substances such as ortho and p-chloronitrobenzene, p-dichlorobenzene, p-chlorotoluene and m-dinitrobenzene fail to react. The presence of alkyl groups in the nucleus, however, counteracts the influence of these substituents. Vavon et al. (Bull. Soc. Chem., 1939, 6, 1025) successfully chloromethylated bromomesitylene.

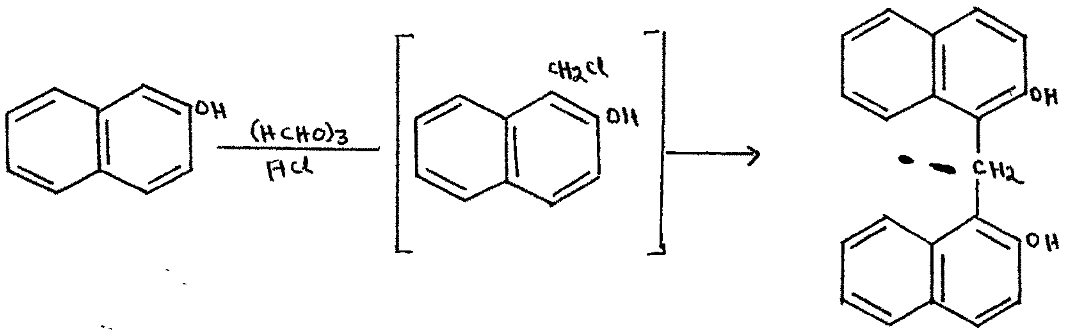
Ketones are generally unreactive. Fuson and McKeever (J. Am. Chem. Soc., 1940, 62, 784) found that benzophenone could not be chloromethylated. Stephen et al. (loc.cit.) failed to chloromethylate anthraquinone. Here also the presence of alkyl group in the nucleus counteracts this influence. Thus Fuson and McKeever (loc.cit.) successfully chloromethylated acetomesitylene and 2,4-dimethylacetophenone.

Hydroxyl groups in the nucleus greatly increase~~s~~ the rate of reaction, the condensation proceeding vigorously yielding polymeric products. A suitable device for getting around the difficulty with phenols is to convert them to esters by treatment with ethyl chlorocarbonate. Ethyl aryl carbonates can be chloromethylated easily (Sommelet et al. Compt. rend., 1933, 197, 256 ; 1934, 198, 2256). The activating influence of hydroxyl group may be sufficiently attenuated by a deactivating group such as nitro,carboxyl or acetyl to make a smooth reaction possible. Stoermer and Behn (Ber., 1901, 34, 2455) successfully chloromethylated o-nitrophenol. Buehler,(C.A., 1948, 42, 2244) chloromethylated salicylic acid and obtained the 5-chloromethyl derivative in good yield.

Phenol ethers react smoothly. Phenol ethers and phenolic compounds containing an aldehyde group also react in a satisfactory manner.

Aromatic amines react vigorously but the complex condensation products are invariably the result of the reaction and it has not been possible to isolate simple chloromethylated products derived from these compounds. (Wagner, J. Am. Chem. Soc., 1933, 55, 724).

The most important side reaction is that leading to the formation of the corresponding diaryl methane derivatives. Highly reactive compounds tend to yield this type of products and it is impossible to isolate the intermediate chloromethyl derivative. Castigloni (C.A., 1937, 31, 8528) chloromethylated β-naphthol and obtained the corresponding diaryl methane derivative.



Role of catalysts, solvents and temperature in chloromethylation.

A variety of procedures have been utilised for the chloromethylation. It is normally achieved using formalin. The formaldehyde may be added as formalin (40 %) or it may be generated in the reaction mixture by depolymerisation of paraformaldehyde. Paraformaldehyde is preferred as it can be weighed accurately and is most suitable whenever anhydrous conditions are to be maintained. Blank (Bull. Soc. Chim., 1923, 33, 313) introduced chloromethyl group into aromatic hydrocarbon by means of a mixture of formalin and paraformaldehyde and hydrochloric acid in presence of anhydrous zinc chloride. Catalyst may or may not be required. Among the catalysts which have been found useful are zinc chloride and acetic acid. Sulphuric acid, phosphoric acid and aluminium chloride are also used as catalysts though these catalysts tend to favour the formation of diaryl methane derivatives. Fieser and Seligman (J. Am. Chem. Soc., 1935, 57, 942) found that in the chloromethylation of p-bromotoluene the yield of the chloromethyl product was increased three fold when a little anhydrous aluminium chloride was used with fused zinc chloride. Sommelet (Compt. rend., 1913, 157, 1443) used stannic chloride with success with compounds which normally resist chloromethylation. For liquid substances no diluent is required. For solid substances which do not dissolve in hydrochloric acid a solvent is used. Acetic acid, carbon disulphide, ethylene dichloride and benzene are used as solvents.

A variety of reaction temperatures are used depending on the type of compound to be chloromethylated. Highly reactive compounds react at 0° while temperatures of 60 - 70° are much favoured for less reactive compounds. Sometimes reactions are carried out at 140° and under pressure.

Chloromethylation may be accomplished by the use of chloromethyl ether ($CH_3.O.CH_2Cl$), or dichloromethyl ether ($CH_2Cl.O.CH_2Cl$), the reaction often proceeds in the absence of a catalyst. Stannic chloride may be used as catalyst with less reactive compounds. Carbon disulphide or other indifferent solvent may be used as diluent. The chloromethyl ether is preferably used in excess. The reaction usually proceeds without hydrochloric acid. Vavon et al. (Bull. Soc. Chim., 1939, 6, 1025) studied the effect of substituents on the ease of chloromethylation of benzene by chloromethyl ether in the absence of a catalyst. They found that the rate is increased by CH_3, C_2H_5, C_3H_7, OCH_3 and reduced by Cl, Br, I, CH_2Cl, COOH and nitro group.

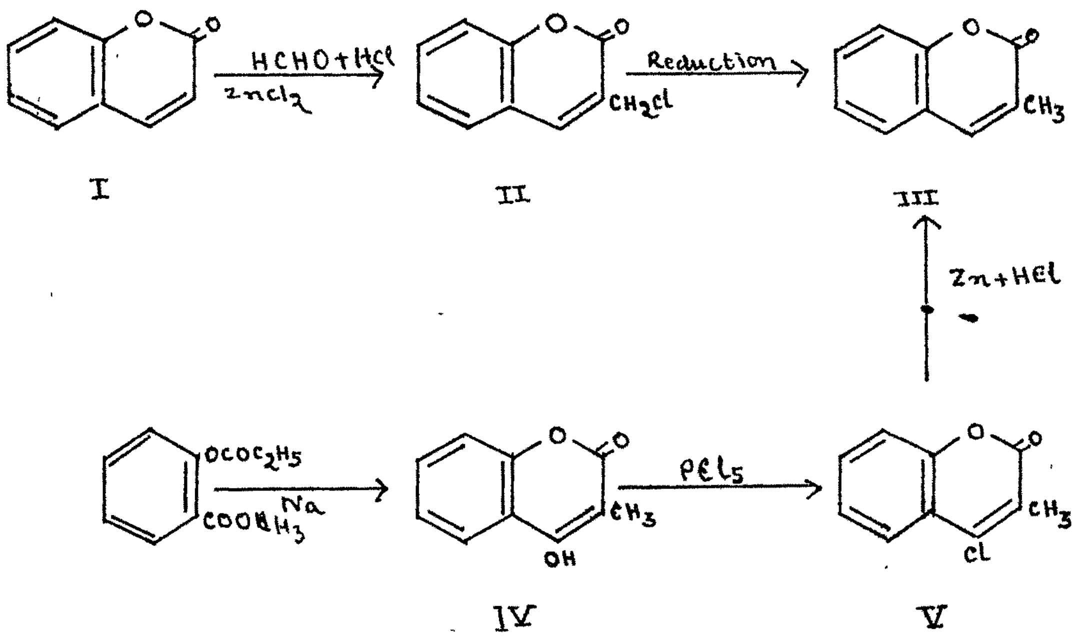
Weisler and Chechak (U.S., 2486542 ; C.A., 1950, 2037) found that an aromatic compound containing one or two aromatic rings can be chloromethylated and the chloromethyl group can be simultaneously reduced if stannous chloride is added to the reaction mixture.

Stoermer and Oetkar (Ber., 1904, 37, 192) prepared 6-chloromethylcoumarin by heating 6-hydroxymethylcoumarin with hydrochloric acid. Direct chloromethylation of coumarins has not been studied at all. In the present work chloromethylation of some typical coumarin derivatives has been studied.

Chloromethylation of Coumarin.

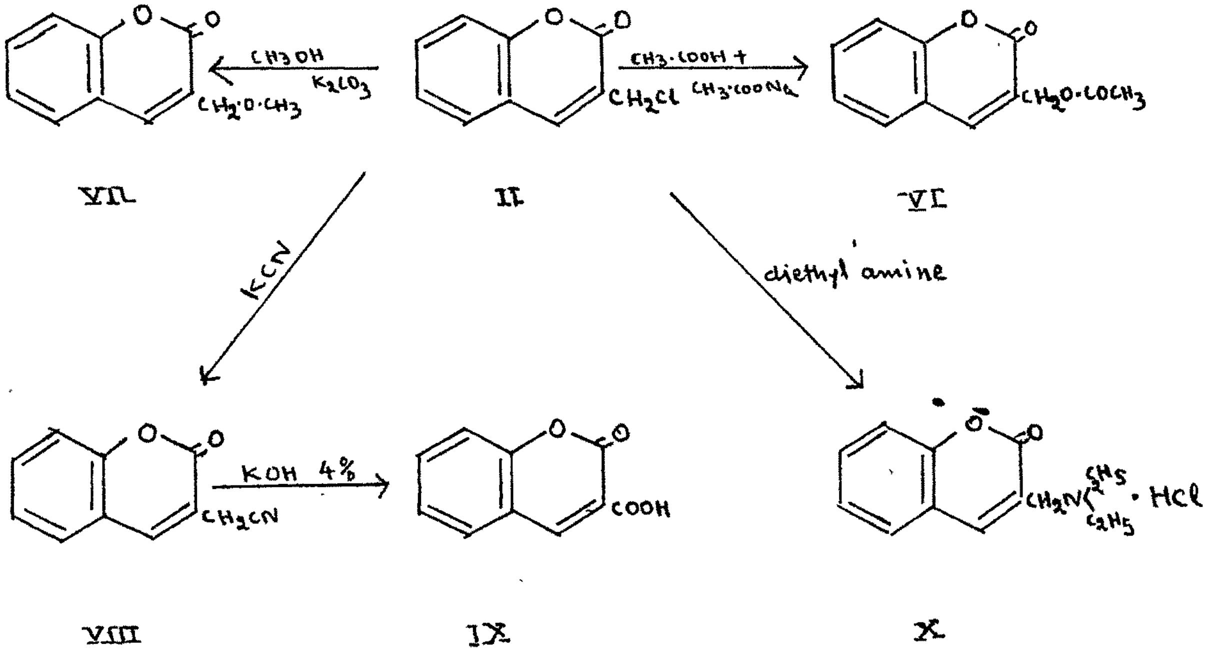
Coumarin (I) could not be chloromethylated using formalin (40 %) and hydrochloric acid. On chloromethylation with two moles of paraformaldehyde in glacial acetic acid solution using anhydrous zinc chloride as catalyst it gave a monochloromethyl derivative. Yield of the chloromethylated product was increased when anhydrous aluminium chloride was used along with zinc chloride. The chloromethylcoumarin on reduction with zinc and acetic acid gave a product which was found, on direct comparison, to be the 3-methylcoumarin. Therefore the structure of 3-chloromethylcoumarin (II) has been assigned to the chloromethyl~~ated~~ product. 3-Methylcoumarin required for comparison was prepared according to the method of Mentzer and Meunier (Bull.Soc.Chim., 1943,10,356-361; C.A. 1944,38,2649) as follows.

Methyl propionylsalicylate when treated with



sodium at 165° gave 3-methyl-4-hydroxycoumarin. On treatment with phosphorus pentachloride it gave 3-methyl-4-chlorocoumarin which on reduction with zinc and hydrochloric acid gave 3-methylcoumarin (III). Simonis (Ber., 1915,48, 1583) prepared 3-methylcoumarin by condensing phenol with α-methyl malic acid using sulphuric acid as condensing agent.

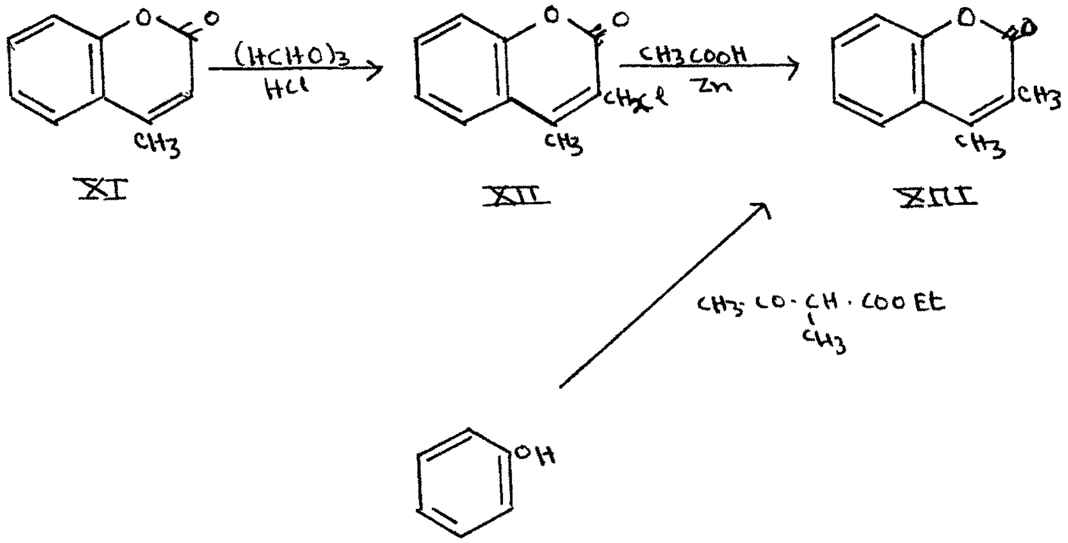
On heating with acetic acid in presence of fused sodium acetate (II) gave the 3-acetoxymethylcoumarin (VI). On heating with magnesium methoxide or with methyl alcohol in presence of anhydrous potassium carbonate it gave 3-methoxymethylcoumarin (VII). When heated with aqueous potassium cyanide it gave the 3-cyanomethylcoumarin (VIII) which on hydrolysis with potassium hydroxide solution (4 %) gave the known coumarin-3-acetic acid (IX). D~~a~~ey and



Y.Sankaranarayanan (J. Indian Chem. Soc., 1931, 8, 817) who prepared the same acid by heating salicylaldehyde with dry sodium succinate and succinic anhydride at 170° reported the same melting point. When heated with diethyl amine, (II) gave 3-diethylaminomethylcoumarin hydrochloride (X). The dichloromethyl derivative of (I) could not be obtained even on chloromethylation with large excess of paraformaldehyde.

Chloromethylation of 4-Methylcoumarin.

4-Methylcoumarin (XI) on chloromrthylation in acetic acid solution (80 %) with one mole of paraformaldehyde gave a monochloromethyl derivative. The yield of the monochloromethyl derivative was considerably increased when anhydrous zinc chloride was used as a catalyst. The compound was assigned the 3-chloromethyl-4-methylcoumarin structure (XII) as on reduction with zinc and acetic acid it gave

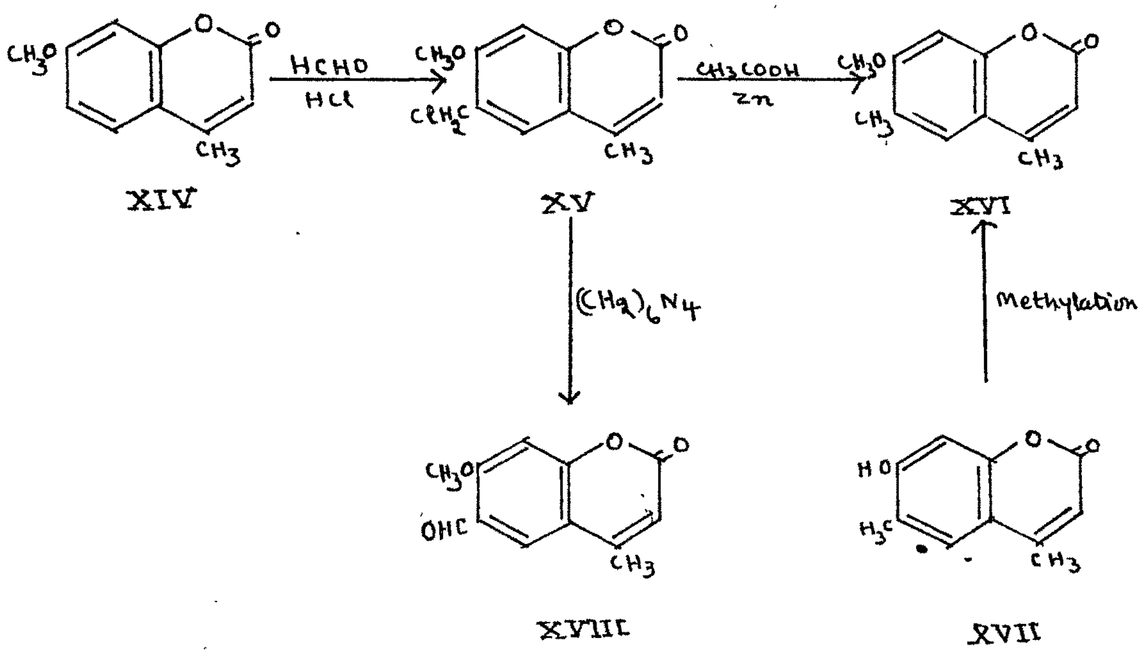


the known 3,4-dimethylcoumarin (XIII). The 3,4-dimethylcoumarin required for the purpose was prepared according to Peters and Simonis (Ber., 1908,41,830) by condensing phenol with ethyl-α-methyl acetoacetate in presence of sulphuric acid.

The acetoxymethyl and methoxymethyl derivatives were prepared as before. On chloromethylation with excess of paraformaldehyde (XI) did not give any dichloromethyl derivative.

Chloromethylation of 7-methoxy-4-methylcoumarin.

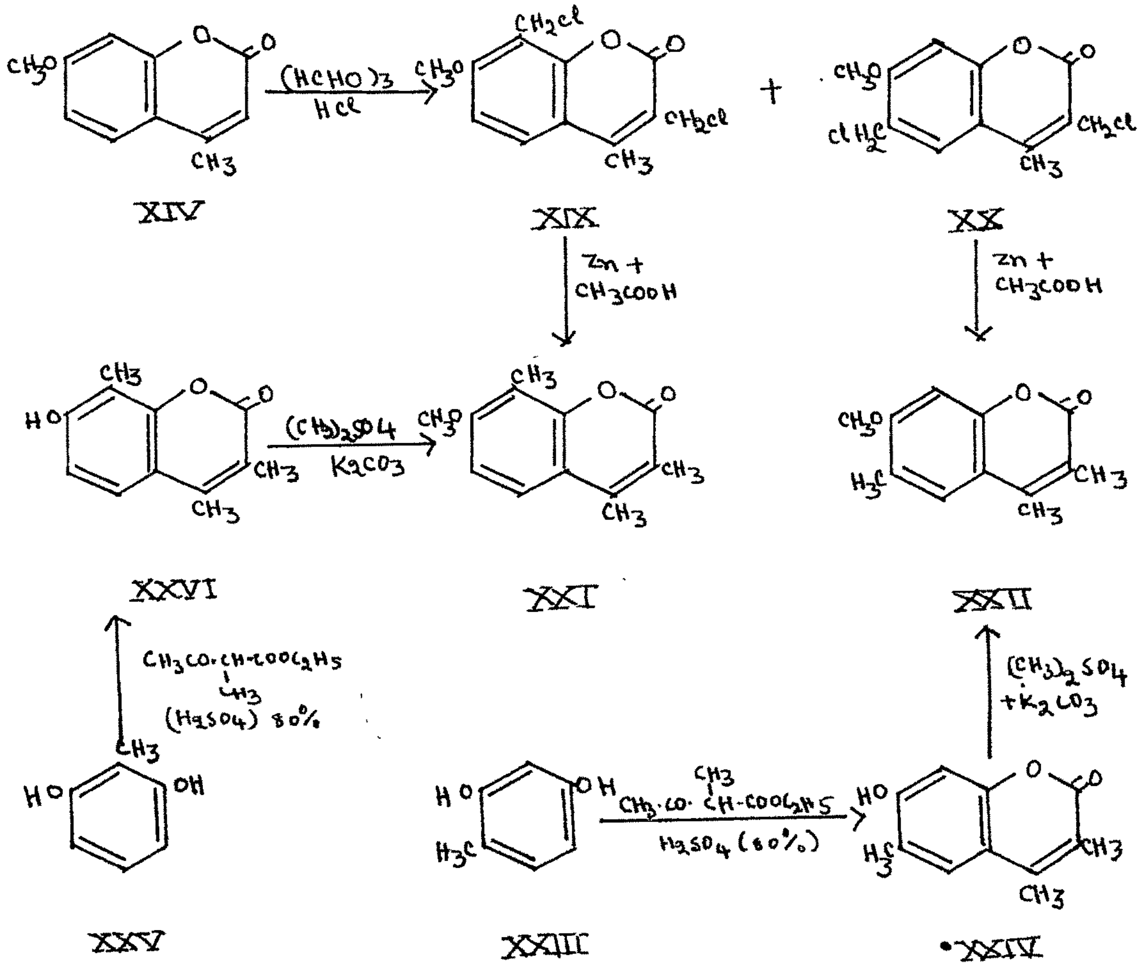
7-Methoxy-4-methylcoumarin (XIV) on chloromethylation with one mole of paraformaldehyde gave a



mixture of various products from which only one monochloromethyl derivative could be isolated in a pure form. 7-Methoxy-6-chloromethyl-4-methylcoumarin structure (XV) has been assigned to this product as on reduction it gave a product which was found to be identical with the methyl ether (XVI) of 7-hydroxy-4,6-dimethylcoumarin prepared from 4-methylresorcinol and ethyl acetoacetate (Yanagita Ber., 1938,71,2269).

The acetoxymethyl and methoxymethyl derivatives were obtained as before. With aqueous potassium cyanide the chloromethylcoumarin (XV) gave 7-methoxy-6-cyanomethyl-4-methylcoumarin which on hydrolysis with potassium hydroxide solution (10 %) yielded 7-methoxy-4-methylcoumarin-6-acetic acid. When (XV) in chloroform solution was treated with hexamethylene tetramine (Sommelet reaction) the hitherto unknown 7-methoxy-6-formyl-4-methylcoumarin (XVIII) was obtained. It was characterised by preparing its 2,4-dinitrophenylhydrazone. Direct formylation of 7-hydroxy-4-methylcoumarin with hexamethylene tetramine leads to the formation of the 8-formyl derivative (Seshadri and Rangaswami Proc.Indian Acad.Sci.,1937,6A,112).When heated in acetone solution with diethyl amine in presence of anhydrous potassium carbonate the chloromethyl coumarin (XV) gave 7-methoxy-6-diethylaminomethyl-4-methylcoumarin.

On chloromethylation with two moles of paraformaldehyde 7-methoxy-4-methylcoumarin (XIV) gave a mixture of two dichloromethyl derivatives : (A) m.p.198° and (B) m.p.195-198°. The two dichloromethyl derivatives were separated by fractional crystallisations from benzene solution. The product (A) being sparingly soluble comes out first in the form of needles. The product (B) was isolated from the filtrate in the form of buds. These dichloromethyl derivatives have nearly the same melting points but their mixed melting point was depressed by over 20°. (A) on reduction gave a product which was found to be identical, on direct comparison, with 7-methoxy-3,4,8-trimethylcoumarin (XXI) synthesised from 2-methylresorcinol by condensation

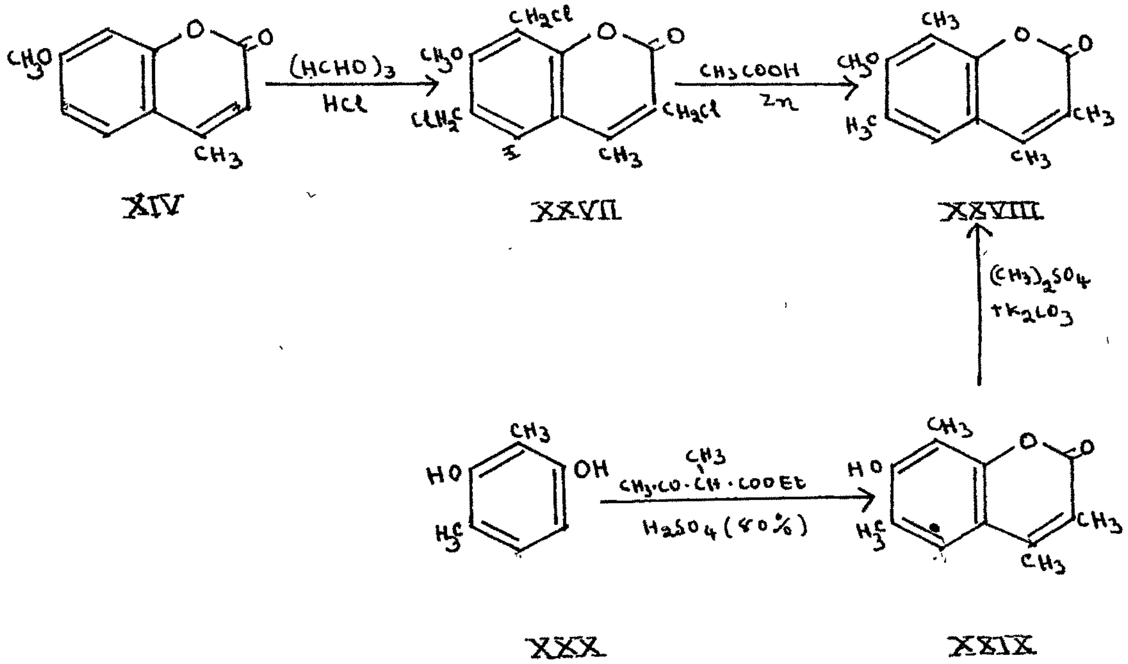


with ethyl-α-methyl acetoacetate in the presence of sulphuric acid and subsequent methylation of the hydroxycoumarin formed. 7-Methoxy-3,8-dichloromethyl-4-methylcoumarin (XIX) structure has therefore been assigned to the product (A). The product (B) on reduction gave a product identical with 7-methoxy-

3,4,6-trimethylcoumarin (XXII) synthesised by condensing 4-methylresorcinol with ethyl-α-methyl acetoacetate and subsequent methylation of the hydroxycoumarin formed. The product (B) is therefore 7-methoxy-3,6-dichloromethyl-4-methylcoumarin (XX).

The diacetoxymethyl and the dimethoxymethyl derivatives of both (XIX) and (XX) have been prepared as before.

7-Methoxy-4-methylcoumarin (XIV) on chloromethylation in ethylene chloride solution in presence of zinc chloride gave a trichloromethyl derivative. The same trichloromethyl derivative could also be obtained on further



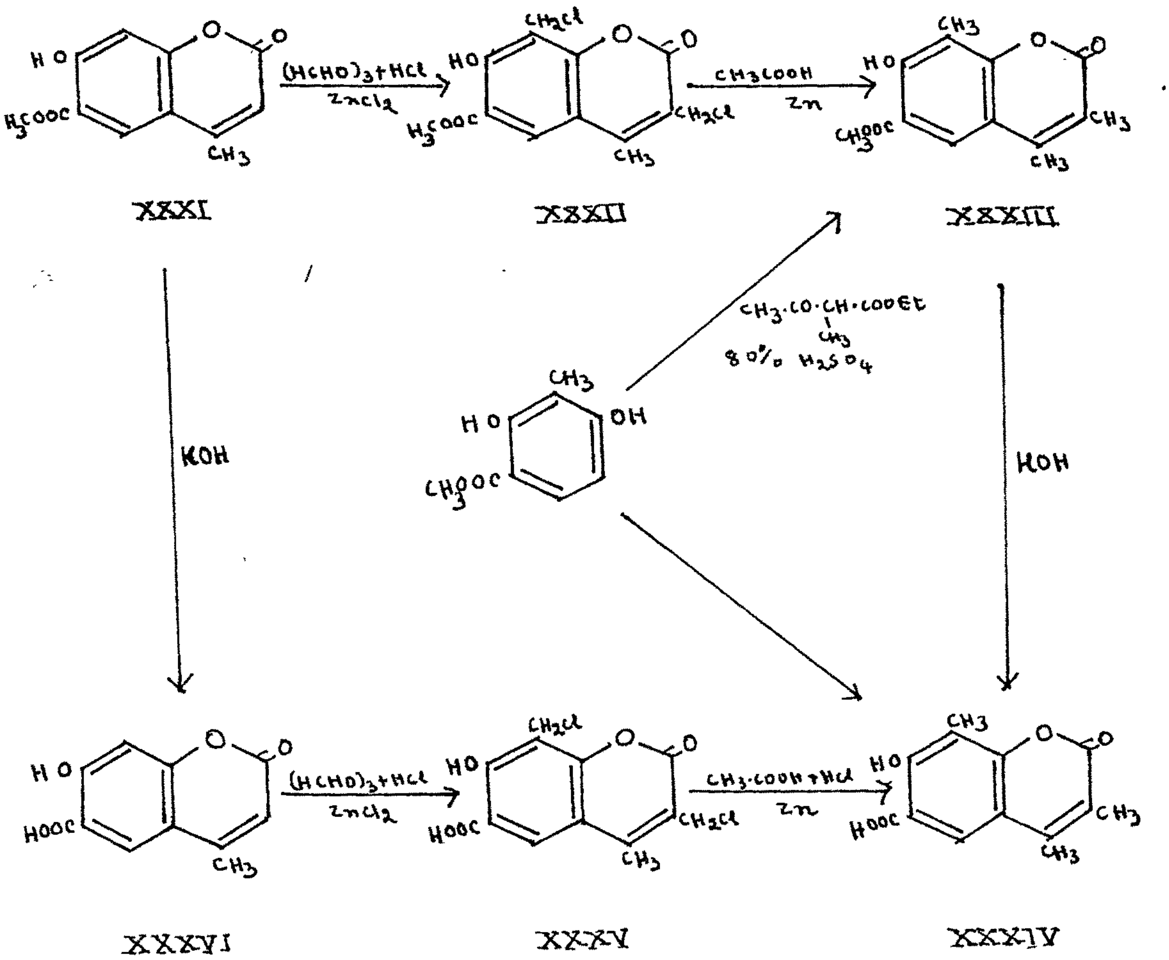
chloromethylation of the above dichloromethyl derivatives. It must be 7-methoxy-3,6,8-trichloromethyl-4-methylcoumarin

(XXVII) as on reduction it gave 7-methoxy-3,4,6,8-tetramethylcoumarin (XXVIII) which was synthesised by the Pechmann condensation of 2,4-dimethylresorcinol with ethyl-α-methyl acetoacetate in the presence of sulphuric acid and subsequent methylation of the hydroxycoumarin (XXIX) formed.

The triacetoxymethyl and trimethoxymethyl derivatives of (XXVII) have been prepared.

Chloromethylation of methyl-7-hydroxy-4-methylcoumarin-6-carboxylate and the corresponding acid.

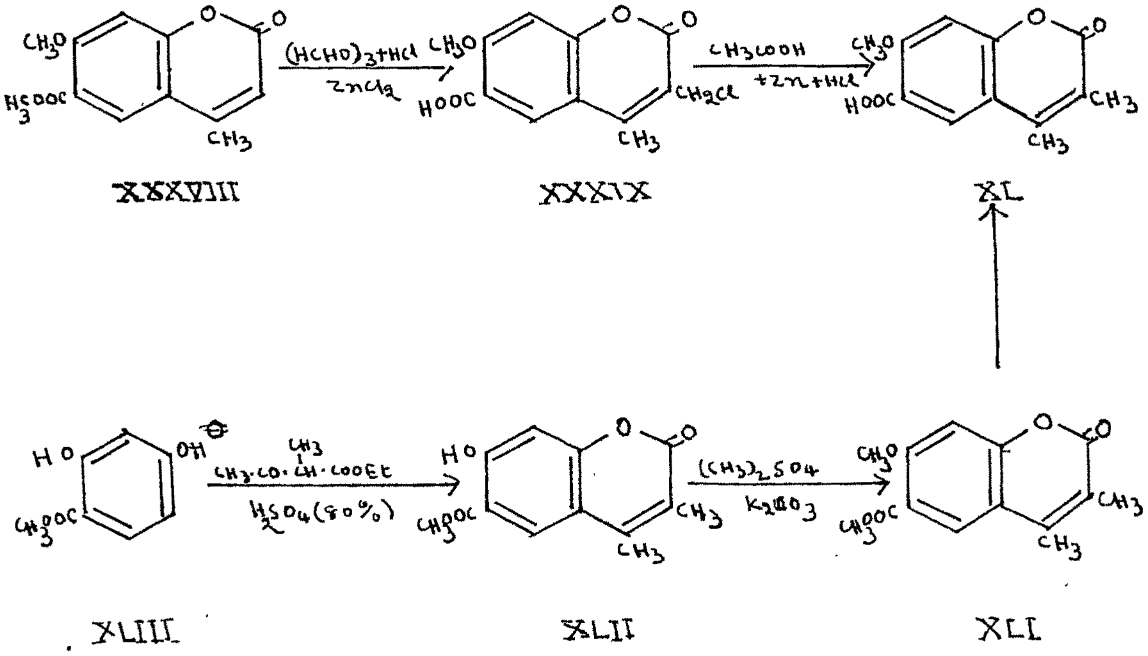
Methyl-7-hydroxy-4-methylcoumarin-6-carboxylate (XXXI) on chloromethylation in acetic acid (80 %) without a catalyst gave a mixture of products from which no pure product could be isolated. Chloromethylation with one mole of paraformaldehyde in presence of anhydrous zinc chloride ~~it~~ gave directly the dichloromethyl derivative, a monochloromethyl derivative could not be isolated. Yield of the dichloromethyl derivative was increased when excess of paraformaldehyde was used. The dichloromethyl derivative on reduction gave methyl-7-hydroxy-3,4,8-trimethylcoumarin-6-carboxylate (XXXIII) synthesised for comparison by condensing methyl-2,4-dihydroxy-3-methylbenzoate with ethyl-α-methyl acetoacetate in the presence of sulphuric acid. The dichloromethyl derivative is therefore methyl-7-hydroxy-3,8-dichloromethyl-4-methylcoumarin-6-carboxylate (XXXII). Methyl-7-hydroxy-3,4,8-trimethylcoumarin-6-carboxylate was hydrolysed to the corresponding acid which on decarboxylation yielded ~~the~~ 7-hydroxy-3,4,8-trimethylcoumarin (XXVI) described earlier. The derivatives such as diacetoxymethyl, dimethoxymethyl and dicyanomethyl of the dichloromethylcoumarin (XXXII) have been prepared.



7-Hydroxy-4-methylcoumarin-6-carboxylic acid (XXXVI) on chloromethylation with one mole or with excess of of paraformaldehyde in presence of anhydrous zinc chloride gave directly the dichloromethyl derivative. No monochloromethyl derivative could be isolated. This on reduction with zinc and hydrochloric acid gave 7-hydroxy-3,4,8-trimethylcoumarin-6-carboxylic acid (XXXIV) mentioned earlier.

The dichloromethyl derivative hence was 7-hydroxy-3,8-dichloromethyl-4-methylcoumarin-6-carboxylic acid (XXXV). With methyl alcohol in presence of sulphuric acid it gave methyl-7-hydroxy-3,8-dimethoxymethyl-4-methylcoumarin-6-carboxylate.

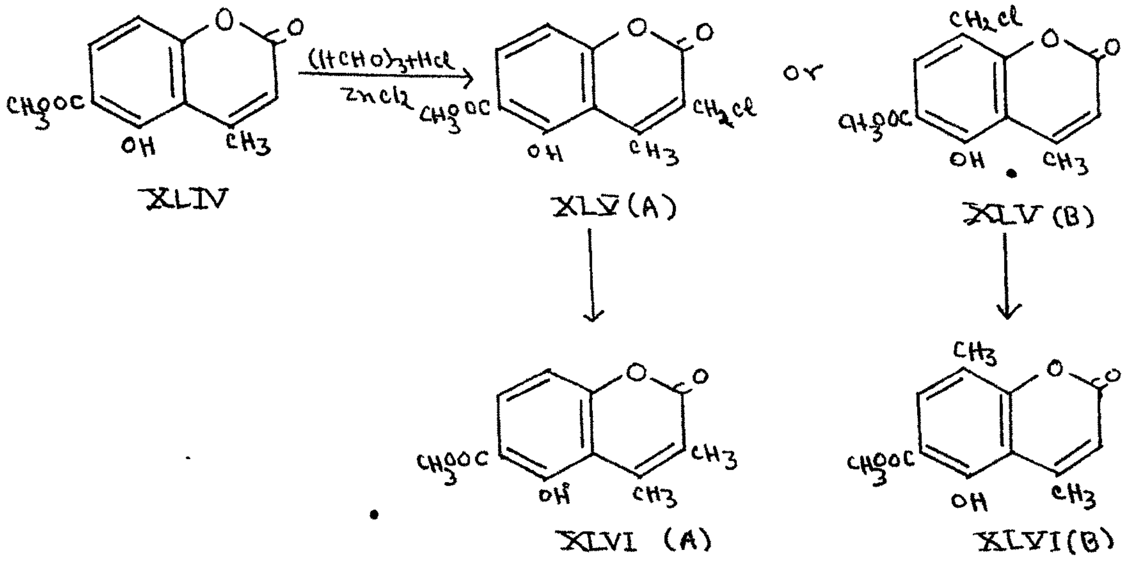
Methyl-7-methoxy-4-methylcoumarin-6-carboxylate on chloromethylation with one mole or with excess of paraformaldehyde in presence of anhydrous zinc chloride gave a monochloromethyl acid. No further chloromethylation was possible. The monochloromethyl derivative on reduction with zinc and hydrochloric acid gave 7-methoxy-3,4-dimethylcoumarin-6-carboxylic acid. This was synthesised by hydrolysing the known methyl-7-methoxy-3,4-dimethylcoumarin-6-carboxylate (XLI) (Sethna and Shah J. Indian Chem. Soc., 1938, 15, 383).



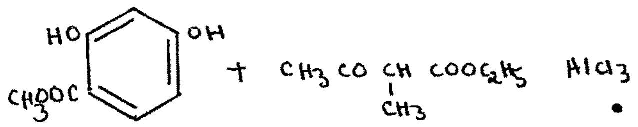
The monochloromethyl derivative is therefore 7-methoxy-3-chloromethyl-4-methylcoumarin-6-carboxylic acid (XXXIX) . With methyl alcohol in presence of sulphuric acid it gave methyl-7-methoxy-3-methoxymethyl-4-methylcoumarin-6-carboxylate.

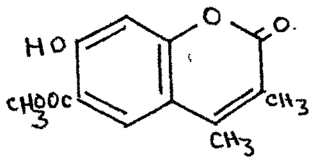
Chloromethylation of some 5-hydroxy-4-methylcoumarin derivatives and their methyl ethers.

Methyl-5-hydroxy-4-methylcoumarin-6-carboxylate (XLIV) on chloromethylation with one mole of paraformaldehyde in presence of anhydrous zinc chloride gave a monochloromethyl derivative. This was reduced to the corresponding methyl derivative with zinc and acetic acid. The chloromethyl group can enter either the 3-position or the 8-position. Its reduction product must have therefore either the 3,4-dimethyl structure (XLVI A) or the 4,8-dimethyl structure (XLVI B). The reduction product was found on direct comparison to be different from methyl-5-hydroxy-3,4-dimethylcoumarin-6-carboxylate (XLVI A) and must have therefore the alternate structure (XLVI B) and the chloromethyl derivative must have the structure (XLV B).

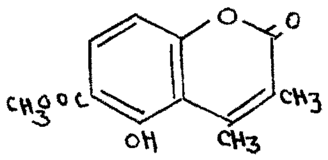


Methyl-5-hydroxy-3,4-dimethylcoumarin-6-carboxylate mentioned above was synthesised as follows : Methyl-β-resorcylate was condensed with ethyl-α-methyl acetoacetate in presence of aluminium chloride when two products were obtained which were separated by fractional crystallisations from rectified spirit. One product gave intense blue fluorescence with alkali and was found to be identical with methyl-7-hydroxy-3,4-dimethylcoumarin-6-carboxylate (XLVII A) synthesised by Sethna and Shah (J. Indian Chem. Soc., 1938, 15, 383). The other product did not show any fluorescence but gave a deep yellow sodium salt with alkali. It was therefore a 5-hydroxycoumarin derivative. Of the two possible structures viz. methyl-5-hydroxy-3,4-dimethylcoumarin-6-carboxylate (XLVII B) and methyl-5-hydroxy-3,4-dimethylcoumarin-8-carboxylate (XLVII C) the former structure has been assigned to the product because it gave a deep reddish brown colour with alcoholic ferric chloride. This is supported by the work of Sethna, Shah and Shah (J. Chem. Soc., 1938, 228) on the condensation of methyl-β-resorcylate with ethyl acetoacetate in presence of anhydrous aluminium chloride.

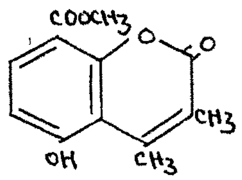




XLVII (A)



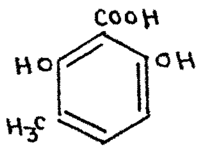
XLVII (B)



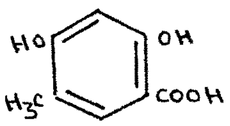
XLVII(C)

Methyl-5-hydroxy-4,8-dimethylcoumarin-6-carboxylate was also synthesised by another method given below.

4-Methylresorcinol on carboxylation gave a mono carboxylic acid. This would have either structure (XLVIII A) or (XLVIII B).



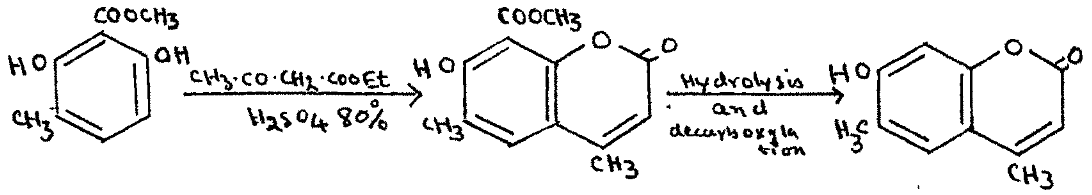
XLVIII (A)



XLVIII (B)

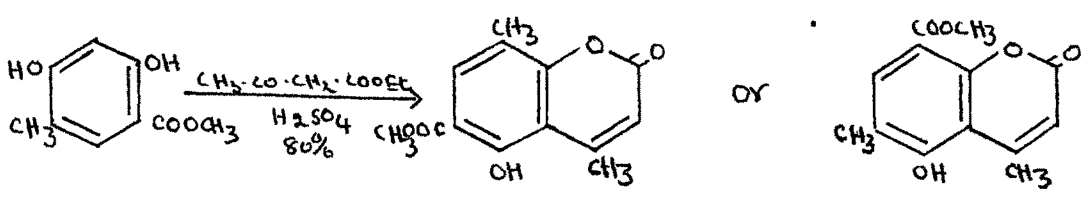
The methyl ester of (XLVIII A) on Pechmann condensation with ethyl acetoacetate would give methyl-7-hydroxy-4,6-dimethylcoumarin-8-carboxylate (XLIX) which would give fluorescence and on hydrolysis and decarboxylation would give the known 7-hydroxy-4,6-dimethylcoumarin (L). But the product actually obtained on Pechmann condensation did not show any fluorescence but gave a deep yellow solution with alkali indicating that it was a 5-hydroxycoumarin derivative. The acid therefore must have the alternate structure (XLVIII B).

The methyl ester of (XLVIII B) on Pechmann condensation with ethyl acetoacetate would give rise to either methyl-5-hydroxy-4,8-dimethylcoumarin-6-carboxylate (LI A) or methyl-5-hydroxy-4,6-dimethylcoumarin-8-carboxylate (LI B). The product obtatined here gave a deep reddish brown colouration with alcoholic ferric chloride and so was (LI A). Further the product obtained was found to be identical with the one obtained on the reduction of the monochloromethyl derivative from methyl-5-hydroxy-4-methylcoumarin-6-carboxylate described above. As the monochloromethyl derivative of (XLIV) could only be 3-chloromethyl or the 8-chloromethyl it cannot give the 4,6-dimethylcoumarin derivative on reduction. Further the methyl ester of (XLVIII B) on Pechmann condensation with ethylacetoacetate cannot give rise to the 6,8-dimethylcoumarin derivative. Both the products must therefore have the methyl-5-hydroxy-4,8-dimethylcoumarin-6-carboxylate (XLVI A) structure. That methyl ester of (XLVIII B) on condensation with ethyl acetoacetate gave the (LI A) is supported by the work of Sethna and Shah (J. Chem. Soc., 1938, 1066) who found that methyl-2,4-dihydroxy-5-ethylbenzoate on condensation with ethyl acetoacetate in presence of aluminium chloride gave methyl-5-hydroxy-4-methyl-8-ethylcoumarin-6-carboxylate.



XLIX

L

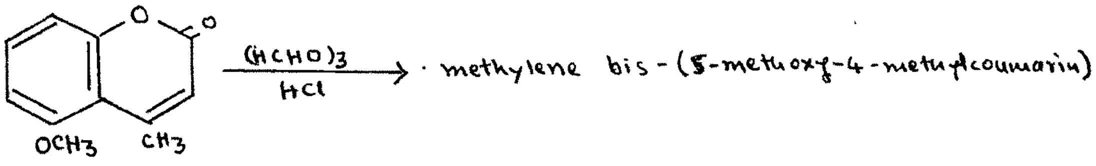


LI (A)

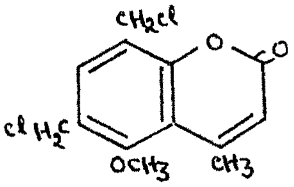
LI (B)

5-Methoxy-4-methylcoumarin on chloromethylation with one mole of paraformaldehyde gave a chlorine free product. The analysis indicated that probably it is ?,?'-methylene bis-(5-methoxy-4-methylcoumarin). It has not been investigated further.

5-Methoxy-4-methylcoumarin (LII) on chloromethylation with excess of paraformaldehyde gave a dichloromethyl derivative. It can have either of the ~~following~~ structures : ~~dichloromethyl~~ (LIII A), ~~dichloromethyl~~ (LIII B) or ~~dichloromethyl~~ (LIII C). These on reduction would give rise to the corresponding methyl derivatives (LIV A), (LIV B) and (LIV C) respectively. That the chloromethyl derivative has the 3,8-dichloromethyl structure (LIII B) has been shown by the following series of reactions.

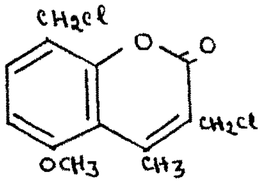


LII



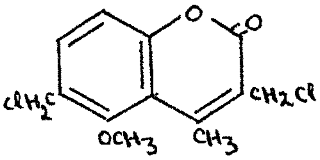
LIII (A)

or

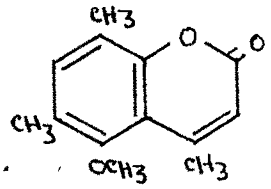


LIII (B)

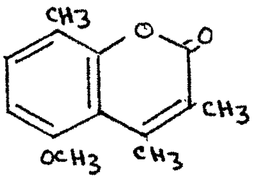
or



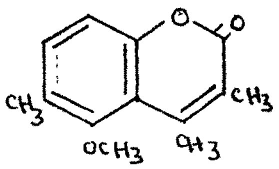
LIII (C)



LIV (A)

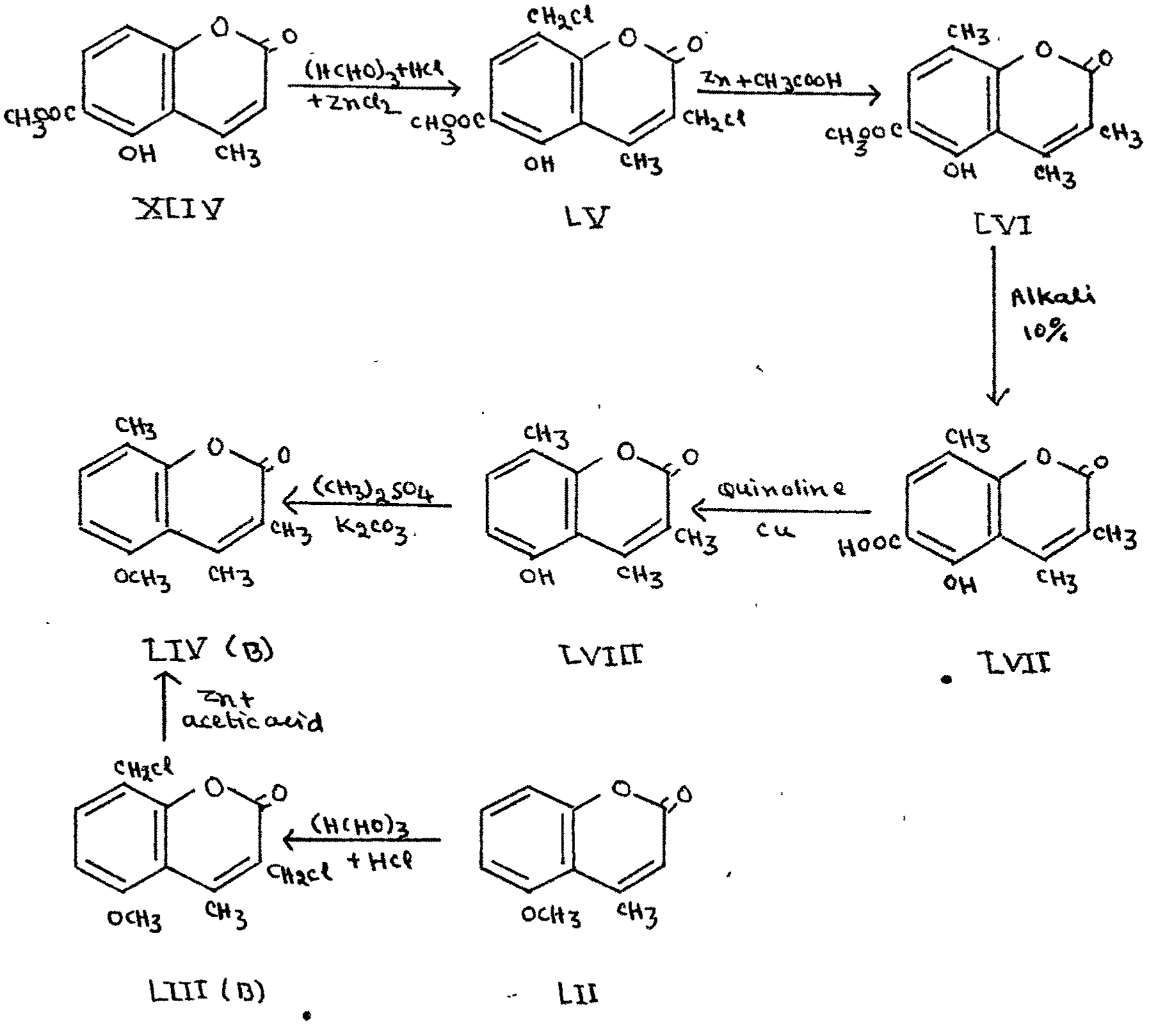


LIV (B)



LIV (C)

Methyl-5-hydroxy-4-methylcoumarin-6-carboxylate (XLIV) on chloromethylation with excess of paraformaldehyde in presence of zinc chloride gave a dichloromethyl derivative which must be methyl-5-hydroxy-3,8-dichloromethyl-4-methylcoumarin-6-carboxylate (LV) as there is no other possibility. This on reduction gave methyl-5-hydroxy-3,4,8-trimethylcoumarin-6-carboxylate (LVI) which on hydrolysis and decarboxylation gave 5-hydroxy-3,4,8-trimethylcoumarin (LVIII). On methylation it gave 5-methoxy-3,4,8-trimethylcoumarin identical with the reduction product of the dichloromethyl derivative from 5-methoxy-4-methylcoumarin described above.



The results obtained in the chloromethylation of coumarins are summarised in the following table.

No.	Substance	Product obtained	Yield %
1.	Coumarin	3-Chloromethyl-	33
2.	4-Methylcoumarin	3-Chloromethyl-	73
3.	7-Methoxy-4-methylcoumarin	6-Chloromethyl-	10
		3,6-Dichloromethyl-	poor
		3,8-Dichloromethyl-	poor
		3,6,8-Trichloromethyl-	22
4.	Methyl-7-hydroxy-4-methylcoumarin-6-carboxylate	3,8-Dichloromethyl-	80
5.	7-Hydroxy-4-methylcoumarin-6-carboxylic acid	3,8-Dichloromethyl-	71
6.	Methyl-7-methoxy-4-methylcoumarin-6-carboxylate	3-Chloromethylcoumarin-6-carboxylic acid	72
7.	5-Methoxy-4-methylcoumarin	?,?'-Methylene-bis-(5-methoxy-4-methylcoumarin)	20
		3,8-dichloromethyl-	27
8.	Methyl-5-hydroxy-4-methylcoumarin-6-carboxylate	8-Chloromethyl-	poor
		3,8-Dichloromethyl-	66

EXPERIMENTAL

Chloromethylation of coumarin :

3-Chloromethylcoumarin. A mixture of coumarin (7.3 g. ; 0.05 mole) in glacial acetic acid (80 ml.), paraformaldehyde (3 g. ; 0.1 mole), anhydrous zinc chloride (7 g. ; 0.05 mole) and anhydrous aluminium chloride (1.3 g. ; 0.01 mole) was treated with dry hydrochloric acid gas at 100° for 3 hours. The reaction mixture was then cooled and diluted with water till turbidity appeared. It was then left overnight in a refrigerator. The separated product was then filtered,washed with plenty of water and dried in a vacuum desiccator. It crystallised from benzene-petroleum ether mixture in small needles,m.p.111°. Yield 1.2 g.

The compound has an irritant action on the skin. The original mother liquor from the reaction mixture on further dilution gave an impure product from which no other product than the original coumarin could be isolated in a pure state.

Analysis :

8.63 mg. of the substance gave 19.47 mg. of carbon dioxide and 2.71 mg. of water.

14.08 mg. of the same substance gave 10.24 mg. of silver chloride.

Found : C = 61.51 % ; H = 3.52 % ; Cl = 17.99 %.

$C_{10}H_7O_2Cl$ requires : C = 61.69 % ; H = 3.59 % ; Cl = 18.30 %.

3-Acetoxymethylcoumarin :

3-Chloromethylcoumarin (0.5 g.) in glacial acetic acid (10 ml.) was refluxed with fused sodium acetate (1 g.) for one hour. The reaction mixture was then poured in cold water and the separated product crystallised from dilute acetic acid in needles,m.p.105-106°.

Analysis :

9.18 mg. of the substance gave 22.26 mg. of carbon dioxide and 3.44 mg. of water.

Found : C = 66.17 % ; H = 4.19 %.

$C_{12}H_{10}O_4$ requires : C = 66.05 % ; H = 4.58 %.

3-Methoxymethylcoumarin :

3-Chloromethylcoumarin (0.5 g.) in methyl alcohol (10 ml.) was refluxed on a steam bath with anhydrous potassium carbonate for 4 hours. The mixture was filtered and diluted with water. The product obtained crystallised from dilute alcohol,m.p.126°.

Analysis :

8.63 mg. of the substance gave 21.85 mg. of carbon dioxide and 4.01 mg. of water.

Found : C = 69.11 % ; H = 5.2 %.

$C_{11}H_{10}O_3$ requires : C = 69.47 % ; H = 5.3 %.

3-Methylcoumarin .

3-Chloromethylcoumarin (0.5 g.) in acetic acid (80 % ; 10 ml.) was treated during 1/2 hour at 60-70° with zinc dust (1 g.). The mixture was heated for further one hour, filtered hot and poured in ice-cold water. The separated product was filtered.More product was obtained by extracting the mother liquor with ether. It crystallised from petroleum ether in needles,m.p.90°. Mixed m.p.with 3-methylcoumarin obtained by the reduction of 4-chloro-3-methylcoumarin with zinc and hydrochloric acid according to Mentzer and Meunier (loc.cit.) was not depressed.

3-Cyanomethylcoumarin.

Aqueous potassium cyanide (0.5 g. in 3 ml. water) was slowly added to 3-chloromethylcoumarin (0.5 g.) in alcohol (10 ml.) and the mixture refluxed on a water bath for 2 hours and then diluted with water. The separated product crystallised from dilute alcohol in needles,m.p.148°.

Analysis :

9.52 mg. of the substance gave 24.84 mg. of carbon dioxide and 3.28 mg. of water.

8.32 mg. of the same substance gave 0.564 ml. of nitrogen at t = 33° and p = 756 mm.

Found : C = 71.21 % ; H = 3.85 % ; N = 7.52 %.

$C_{11}H_7O_2N$ requires : C = 71.35 % ; H = 3.81 % ; N = 7.56 %.

Coumarin-3-acetic acid.

3-Cyanomethylcoumarin (1 g.) was refluxed on a steam bath with alcoholic potassium hydroxide solution (10 % ; 10 ml.) for 2 hours. The mixture was then cooled, diluted with water and acidified. The separated product was purified through sodium bicarbonate solution. It crystallised from dilute acetic acid,m.p.150°.

Dey and Sankarnarayanan (loc.cit.) reported the same melting point.

Analysis :

9.86 mg. of the substance gave 23.32 mg. of carbon dioxide and 3.40 mg. of water.

Found : C = 64.54 % ; H = 3.85 %.

$C_{11}H_8O_4$ requires : C = 64.70 % ; H = 3.95 %.

3-Diethylaminomethylcoumarin hydrochloride.

3-Chloromethylcoumarin (1 g.) in diethylamine (10 ml.) was refluxed on a steam bath for 1 hour. The separated diethylamine hydrochloride was filtered and the filtrate evaporated. The residue was then dissolved in alcohol (5 ml.) and the solution saturated with hydrochloric acid. Ether was then added till turbidity appeared and the mixture left overnight. The separated product was recrystallised from chloroform, m.p. 115°.

Analysis :

6.52 mg. of the substance gave 0.303 ml. of nitrogen at t = 32° and p = 757 mm.

16.34 mg. of the same substance gave 8.86 mg. of silver chloride.

Found : N = 5.18 % ; Cl = 13.40 %.

$C_{14}H_{18}O_2NCl$ requires : N = 5.23 % ; Cl = 13.27 %.

Chloromethylation of 4-methylcoumarin :

3-Chloromethyl-4-methylcoumarin. A mixture of 4-methylcoumarin (1.6 g. ; 0.01 mole) in acetic acid (60 % ; 40 ml.) and paraformaldehyde (2.4 g. ; 0.08 mole) was treated with hydrochloric acid gas for 3 hours at 100°.

The mixture was then cooled and diluted with water. The separated product crystallised from benzene-petroleum ether mixture in fine colourless plates, m.p.139-140°. Yield 0.8 g.

Analysis :

9.28 mg. of the substance gave 21.48 mg. of carbon dioxide and 3.33 mg. of water.

15.40 mg. of the same substance gave 10.34 mg. of silver chloride.

Found : C = 63.18 % ; H = 4.02 % ; Cl = 16.61 %.

$C_{11}H_9O_2Cl$ requires : C = 63.30 % ; H = 4.31 % ; Cl = 17.00 %.

3-Acetoxymethyl-4-methylcoumarin.

This was prepared by refluxing the 3-chloromethyl-4-methylcoumarin in acetic acid with fused sodium acetate as before. It crystallised from rectified spirit in needles, m.p.128°.

Analysis :

9.84 mg. of the substance gave 24.42 mg. of carbon dioxide and 4.46 mg. of water.

Found : C = 67.72 % ; H = 5.07 %.

$C_{13}H_{12}O_4$ requires : C = 67.24 % ; H = 5.17 %.

3-Methoxymethyl-4-methylcoumarin.

This was prepared by refluxing the 3-chloromethyl-4-methylcoumarin in methyl alcohol with anhydrous potassium carbonate as before. It crystallised from rectified spirit in needles, m.p.72°.

Analysis :

10.06 mg. of the substance gave 26.10 mg. of carbon dioxide and 5.18 mg. of water.

Found : C = 70.80 % ; H = 5.76 %.

$C_{12}H_{12}O_3$ requires : C = 70.58 %.; H = 5.88 %.

3,4-Dimethylcoumarin.

3-Chloromethyl-4-methylcoumarin (0.5 g.) in acetic acid (80 % ; 15 ml.) was treated during 1/2 hour at 60-70° with zinc dust (1 g.). The mixture was heated for further 1 hour, filtered hot and poured in cold water. The separated product crystallised from dilute acetic acid in needles,m.p.117°. Mixed m.p.with the product prepared according to the method of Peters and Simonis (loc.cit.) was not depressed.

Chloromethylation of 7-methoxy-4-methylcoumarin : 7-Methoxy-6-chloromethyl-4-methylcoumarin.

A mixture of 7-methoxy-4-methylcoumarin (3.8 g. ; 0.02 mole) in acetic acid (80 % ; 30 ml.) and paraformaldehyde (0.6 g. ; 0.02 mole) was treated with hydrochloric acid gas at 60-70° for one hour. The mixture was left overnight in a refrigerator and the product which separated was filtered,washed with alcohol and crystallised from benzene in fine needles,m.p.246°. Yield 0.4 g.

Analysis :

7.22 mg. of the substance gave 16.09 mg. of carbon dioxide and 3.052 mg. of water.

12.49 mg. of the same substance gave 7.331 mg. of silver chloride.

Found : C = 60.81 % ; H = 4.73 % ; Cl = 14.52 %.

$C_{12}H_{11}O_3Cl$ requires : C = 60.37 % ; H = 4.61 % ; Cl = 14.88 %.

The acetoxymethyl derivative was prepared by refluxing the above chloromethyl coumarin in acetic acid with fused sodium acetate as before. It crystallised from rectified spirit in needles, m.p. 191°.

Analysis :

9.00 mg. of the substance gave 21.06 mg. of carbon dioxide and 4.4 mg. of water.

Found : C = 63.86 % ; H = 5.47 %.

$C_{14}H_{14}O_5$ requires : C = 64.12 % ; H = 5.34 %.

The methoxymethyl derivative was prepared by refluxing the above chloromethyl coumarin in methyl alcohol with anhydrous potassium carbonate as before. It crystallised from rectified spirit in needles, m.p. 136°.

Analysis :

9.41 mg. of the substance gave 22.90 mg. of carbon dioxide and 4.97 mg. of water.

Found : C = 66.42 % ; H = 6.02 %.

$C_{13}H_{14}O_4$ requires : C = 66.65 % ; H = 6.02 %.

7-Methoxy-4,6-dimethylcoumarin.

7-Methoxy-6-chloromethyl-4-methylcoumarin (0.5 g.) in acetic acid (80 % ; 20 ml.) was treated during half hour at 60-70° with zinc dust (1 g.). The mixture was heated for further one hour, filtered hot and poured in cold water. The separated solid crystallised from dilute acetic acid in needles, m.p. 181°. It was found to be identical, on direct comparison, with the product obtained on methylation of the known 7-hydroxy-4,6-dimethylcoumarin prepared according to Yanagita (loc. cit.).

<u>Analysis</u> :

5.01 mg. of the substance gave 12.86 mg. of carbon dioxide and 2.55 mg. of water.

Found : C = 70.08 % ; H = 5.69 %.

$C_{12}H_{12}O_3$ requires : C = 70.58 % ; H = 5.88 %.

7-Methoxy-6-formyl-4-methylcoumarin.

7-Methoxy-6-chloromethyl-4-methylcoumarin (0.5 g.) in chloroform (20 ml.) was treated with dry hexamine (1.2 g.) and the solution refluxed on a water bath. Separation of complex salt started after half an hour and was complete in about 2 hours. It was then filtered and decomposed by boiling for half hour with dilute acetic acid (1:1 ; 20 ml.). The product obtained crystallised from acetic acid in needles, m.p. 256-257°. Yield 0.06 g.

<u>Analysis</u> :

3.48 mg. of the substance gave 8.47 mg. of carbon dioxide and 1.51 mg. of water.

Found : C = 66.25 % ; H = 4.83 %.

$C_{12}H_{10}O_4$ requires : C = 66.05 % ; H = $\overset{4}{\cancel{3}}$.58 %.

<u>The 2,4-dinitrophenylhydrazone</u> prepared as usual was crystallised from acetic acid, m.p. 292°.

Analysis :

7.32 mg. of the substance gave 0.879 ml. of nitrogen at t = 31°C and p = 761 mm.

Found : N = 13.50 %.

$C_{18}H_{14}O_8N_4$ requires : N = 13.52 %.

7-Methoxy-6-cyanomethyl-4-methylcoumarin.

Aqueous potassium cyanide (0.5 g. in 5 ml. water) was slowly added to a suspension of 7-methoxy-6-chloromethyl-4-methylcoumarin (0.5 g.) in alcohol (60 % ; 20 ml.) and the mixture refluxed on a water bath for 2 hours. The solid which separated crystallised from acetic acid in needles, m.p.248-250°.

Analysis :

8.52 mg. of the substance gave 21.28 mg. of carbon dioxide and 4.83 mg. of water.

8.68 mg. of the same substance gave 0.456 ml. of nitrogen at t = 30°C and p = 755 mm.

Found : C = 68.16 % ; H = 4.83 % ; N = 5.88 %.

$C_{13}H_{11}O_3N$ requires : C = 68.11 % ; H = 4.84 % ; N = 6.11 %.

7-Methoxy-4-methylcoumarin-6-acetic acid.

7-Methoxy-6-cyanomethyl-4-methylcoumarin (0.5 g.) was refluxed on a steam bath with alcoholic potassium hydroxide solution (10 % ; 10 ml.) for 2 hours. The product obtained on acidification was purified through sodium bicarbonate solution and crystallised from acetic acid, m.p.247°.

Analysis :

8.64 mg. of the substance gave 19.94 mg. of carbon dioxide and 3.84 mg. of water.

Found : C = 62.98 % ; H = 4.97 %.

$C_{13}H_{12}O_5$ requires : C = 62.90 % ; H = 4.83 %.

7-Methoxy-6-diethylaminomethyl-4-methylcoumarin.

Diethylamine (0.5 ml.) was slowly added to a suspension of the 6-chloromethylcoumarin derivative (0.5 g.) in alcohol (20 ml.) and the mixture refluxed on a water bath for one hour. The product which separated on dilution with water was purified through dilute hydrochloric acid solution. It crystallised from alcohol in the form of buds. It melts to a translucent liquid at 98° which clears up at 130°.

Analysis :

9.34 mg. of the substance gave 23.82 mg. of carbon dioxide and 6.20 mg. of water.

9.62 mg. of the same substance gave 0.436 ml. of nitrogen at t = 30°C and p = 754 mm.

Found : C = 69.61 % ; H = 7.42 % ; N = 5.07 %.

$C_{16}H_{21}O_3N$ requires : C = 69.79 % ; H = 7.69 % ; N = 5.09 %.

(i) 7-Methoxy-3,8-dichloromethyl-4-methylcoumarin.

A mixture of 7-methoxy-4-methylcoumarin (1.9 g. ; 0.01 mole) in acetic acid (80 % ; 50 ml.) and paraformaldehyde (0.7 g. ; 0.023 mole) was treated with hydrochloric acid gas at 60-70° for 2 hours and the mixture was left overnight at room temperature. The next day the separated product was filtered and dried. It was dissolved in benzene by warming and allowed to cool. The 3,8-dichloromethyl derivative started separating in the form of needles. When the other isomer, which separates in the form of buds, started separating, the benzene solution was filtered. The filtrate was treated as described under (ii) later. The residue on recrystallisation from benzene yielded pure 3,8-dichloromethyl derivative, m.p. 198°. The yield was poor.

Analysis :

4.668 mg. of the substance gave 9.298 mg. of carbon dioxide and 1.69 mg. of water.

16.29 mg. of the same substance gave 16.33 mg. of silver chloride.

Found : C = 54.36 % ; H = 4.06 % ; Cl = 24.79 %.

$C_{13}H_{12}O_3Cl_2$ requires : C = 54.35 % ; H = 4.18 % ; Cl = 24.73 %.

The diacetoxymethyl derivative was prepared by refluxing the above 3,8-dichloromethylcoumarin in acetic acid with fused sodium acetate as before. It crystallised from rectified spirit in needles, m.p. 174°.

Analysis :

8.80 mg. of the substance gave 19.80 mg. of carbon dioxide and 3.92 mg. of water.

Found : C = 61.40 % ; H = 4.98 %.

$C_{17}H_{18}O_7$ requires : C = 61.07 % ; H = 5.43 %.

The dimethoxymethyl derivative was prepared by refluxing the above dichloromethylcoumarin derivative in methyl alcohol with anhydrous potassium carbonate as before. It crystallised from benzene-petroleum ether mixture in needles, m.p. 174°.

Analysis :

8.42 mg. of the substance gave 19.90 mg. of carbon dioxide and 4.95 mg. of water.

Found : C = 64.50 % ; H = 6.58 %.

$C_{15}H_{18}O_5$ requires : C = 64.73 % ; H = 6.52 %.

7-Methoxy-3,4,8-trimethylcoumarin.

7-Methoxy-3,8-dichloromethyl-4-methylcoumarin (0.5 g.) in acetic acid (80 % ; 20 ml.) was treated during half an hour at 60-70° with zinc dust (1 g.). The mixture was heated for further one hour, filtered hot and poured in cold water. The separated product crystallised from rectified spirit in needles, m.p. 188-190°. Mixed m.p. with 7-methoxy-3,4,8-trimethylcoumarin synthesised as shown below was not depressed.

Analysis :

4.724 mg. of the substance gave 12.316 mg. of carbon dioxide and 2.560 mg. of water.

Found : C = 71.15 % ; H = 6.07 %.

$C_{13}H_{14}O_3$ requires : C = 71.55 % ; H = 6.42 %.

Pechmann condensation of 2-methylresorcinol with ethyl-α-methyl acetoacetate : 7-Hydroxy-3,4,8-trimethylcoumarin.

A mixture of 2-methylresorcinol (1.24 g.) and ethyl-α-methyl acetoacetate (1.44 g.) was treated with sulphuric acid (80 % ; 10.ml.) and left overnight at room temperature. The product obtained on pouring the reaction mixture in cold water crystallised from rectified spirit in needles,m.p.274°.

Analysis :

8.96 mg. of the substance gave 23.16 mg. of carbon dioxide and 4.58 mg. of water.

Found : C = 70.54 % ; H = 5.72 %.

$C_{12}H_{12}O_3$ requires : C = 70.58 % ; H = 5.88 %.

The methyl ether. Prepared by refluxing 7-hydroxy-3,4,8-trimethylcoumarin in acetone solution with dimethyl sulphate in presence of anhydrous potassium carbonate as usual was crystallised from rectified spirit in needles, m.p.188-190°.

(ii) 7-Methoxy-3,6-dichloromethyl-4-methylcoumarin.

The filtrate from above experiment (i) was cooled further when the 3,6-dichloromethyl derivative separated. It was crystallised from benzene-petroleum ether mixture in fine colourless buds,m.p.195-198°. Yield was poor.

Analysis :

8.56 mg. of the substance gave 17.02 mg. of carbon dioxide and 3.00 mg. of water.

10.756 mg. of the same substance gave 10.688 mg. of silver chloride.

Found : C = 54.28 % ; H = 3.92 % ; Cl = 24.60 %.

$C_{13}H_{12}O_3Cl_2$ requires : C = 54.35 % ; H = 4.18 % ; Cl = 24.73 %.

The diacetoxymethyl derivative prepared as before crystallised from rectified spirit in needles, m.p. 180°.

Analysis :

4.04 mg. of the substance gave 9.00 mg. of carbon dioxide and 2.05 mg. of water.

Found : C = 60.72 % ; H = 5.68 %.

$C_{17}H_{18}O_7$ requires : C = 61.07 % ; H = 5.38 %.

The dimethoxymethyl derivative prepared as before was crystallised from benzene-petroleum ether mixture, m.p. 169°.

Analysis :

8.23 mg. of the substance gave 19.40 mg. of carbon dioxide and 4.77 mg. of water.

Found : C = 64.32 % ; H = 6.48 %.

$C_{15}H_{18}O_5$ requires : C = 64.73 % ; H = 6.52 %.

7-Methoxy-3,4,6-trimethylcoumarin.

The above 3,6-dichloromethyl derivative (0.5 g.) in acetic acid (80 % ; 20 ml.) and hydrochloric acid (1 ml.) was reduced with zinc dust as in the case of isomeric 3,8-dichloromethyl derivative. The product obtained was washed with petroleum ether (60-80°) and then crystallised from dilute acetic acid in needles, m.p. 195°. Mixed m.p. with 7-methoxy-3,4,6-trimethylcoumarin prepared as shown below was not depressed.

Analysis :

3.262 mg. of the substance gave 8.480 mg. of carbon dioxide and 1.950 mg. of water.

Found : C = 70.95 % ; H = 6.68 %.

$C_{13}H_{14}O_3$ requires : C = 71.55 % ; H = 6.42 %.

Pechmann condensation of 4-methylresorcinol with ethyl-α-methyl acetoacetate : 7-Hydroxy-3,4,6-trimethylcoumarin.

A mixture of 4-methylresorcinol (1.24 g.) and ethyl-α-methyl acetoacetate (1.44 g.) was treated with sulphuric acid (80 % ; 10 ml.). The product obtained on working up the reaction mixture as before crystallised from rectified spirit in needles,m.p.266°.

Analysis :

3.458 mg. of the substance gave 8.904 mg. of carbon dioxide and 1.668 mg. of water.

Found : C = 70.27 % ; H = 5.39 %.

$C_{12}H_{12}O_3$ requires : C = 70.58 % ; H = 5.88 %.

The methyl ether. Prepared by refluxing 7-hydroxy-3,4,6-trimethylcoumarin in acetone solution with dimethyl sulphate in presence of anhydrous potassium carbonate was crystallised from rectified spirit in needles,m.p.195°.

7-Methoxy-3,6,8-trichloromethyl-4-methylcoumarin.

A mixture of 7-methoxy-4-methylcoumarin (1.9 g. ; 0.01 mole) in ethylene chloride (50 ml.),paraformaldehyde (2.4 g. ; 0.08 mole) and anhydrous zinc chloride (1.39 g.) was treated with hydrochloric acid gas at 60° for 4 hours. More ethylene chloride was added from time to time. On cooling the reaction mixture some pasty mass separated which was filtered and the filtrate diluted with petroleum ether.

The separated product crystallised from benzene-petroleum ether mixture in needles, m.p. 168°. Yield 1.6 g.

Analysis :

8.91 mg. of the substance gave 16.37 mg. of carbon dioxide and 3.042 mg. of water.

13.36 mg. of the same substance gave 17.29 mg. of silver chloride.

Found : C = 50.13 % ; H = 3.82 % ; Cl = 32.02 %.

$C_{14}H_{13}O_3Cl_3$ requires : C = 50.06 % ; H = 3.87 % ; Cl = 31.74 %.

The same product was obtained when a mixture of 7-methoxy-3,8-, and 7-methoxy-3,6-dichloromethyl-4-methylcoumarin, described earlier, in acetic acid (80 %) and paraformaldehyde (excess) was treated with hydrochloric acid gas at 60-70° for 4 hours.

The triacetoxymethyl derivative prepared as before was crystallised from rectified spirit in needles, m.p. 203°.

Analysis :

7.92 mg. of the substance gave 17.13 mg. of carbon dioxide and 3.69 mg. of water.

Found : C = 59.02 % ; H = 5.22 %.

$C_{20}H_{22}O_9$ requires : C = 59.11 % ; H = 5.46 %.

The trimethoxymethyl derivative prepared as before was crystallised from rectified spirit in needles, m.p. 182°.

Analysis :

8.79 mg. of the substance gave 20.55 mg. of carbon dioxide and 5.09 mg. of water.

Found : C = 63.80 % ; H = 6.48 %.

$C_{17}H_{22}O_6$ requires : C = 63.34 % ; H = 6.88 %.

7-Methoxy-3,4,6,8-tetramethylcoumarin.

7-Methoxy-3,6,8-trichloromethyl-4-methylcoumarin (0.5 g.) in acetic acid (80 % ; 20 ml.) was reduced with zinc dust (1 g.) as before. The product crystallised from rectified spirit in needles,m.p.131°. Mixed m.p.with 7-methoxy-3,4,6,8-tetramethylcoumarin synthesised as shown below was not depressed.

Analysis :

8.70 mg. of the substance gave 23.08 mg. of carbon dioxide and 5.06 mg. of water.

Found : C = 72.40 % ; H = 6.51 %.

$C_{14}H_{16}O_3$ requires : C = 72.39 % ; H = 6.94 %.

Pechmann condensation of 2,4-dimethylresorcinol with ethyl-α-methyl acetoacetate : 7-Hydroxy-3,4,6,8-tetramethylcoumarin.

A mixture of 2,4-dimethylresorcinol (1.38 g.) and ethyl-α-methyl acetoacetate (1.44 g.) was kept with sulphuric acid (80 % ; 10 ml.) overnight. The product obtained on working up the reaction mixture as before crystallised from rectified spirit in needles,m.p.232°.

Analysis :

9.36 mg. of the substance gave 24.42 mg. of carbon dioxide and 5.12 mg. of water.

Found : C = 71.20 % ; H = 6.12 %.

$C_{13}H_{14}O_3$ requires : C = 71.54 % ; H = 6.47 %.

The methyl ether. Prepared by refluxing 7-hydroxy-3,4,6,8-tetramethylcoumarin in acetone solution with dimethyl sulphate in presence of anhydrous potassium carbonate was crystallised from rectified spirit in needles, m.p. 131°.

Chloromethylation of methyl-7-hydroxy-4-methylcoumarin-6-carboxylate.

Methyl-7-hydroxy-3,8-dichloromethyl-4-methylcoumarin-6-carboxylate : A mixture of methyl-7-hydroxy-4-methylcoumarin-6-carboxylate (2.34 g. ; 0.01 mole) in glacial acetic acid (60 ml.) paraformaldehyde (4.8 g. ; 0.16 mole) and anhydrous zinc chloride (4.1 g. ; 0.03 mole) was treated with hydrochloric acid gas at 100° for one hour. The product which separated on cooling was filtered, washed with alcohol and dried. It crystallised from benzene in needles, m.p. 206°. Yield 2.5 g.

Analysis :

4.80 mg. of the substance gave 9.00 mg. of carbon dioxide and 1.56 mg. of water.

14.51 mg. of the same substance gave 12.56 mg. of silver chloride.

Found : C = 51.26 % ; H = 3.63 % ; Cl = 21.41 %.

$C_{14}H_{12}O_5Cl_2$ requires : C = 50.75 % ; H = 3.62 % ; Cl = 21.45 %.

The acetoxymethyl derivative prepared as before was crystallised from rectified spirit in needles, m.p. 198°. di/

Analysis :

9.68 mg. of the substance gave 20.32 mg. of carbon dioxide and 3.78 mg. of water.

Found : C = 57.29 % ; H = 4.36 %.

$C_{18}H_{18}O_9$ requires : C = 57.14 % ; H = 4.76 %.

The dimethoxymethyl derivative prepared as before crystallised from rectified spirit in needles, m.p. 138°.

Analysis :

4.06 mg. of the substance gave 8.84 mg. of carbon dioxide and 1.99 mg. of water.

Found : C = 59.42 % ; H = 5.48 %.

$C_{16}H_{18}O_7$ requires : C = 59.62 % ; H = 5.59 %.

Methyl-7-hydroxy-3,4,8-trimethylcoumarin-6-carboxylate.

Methyl-7-hydroxy-3,8-dichloromethyl-4-methylcoumarin-6-carboxylate (0.5 g.) in acetic acid (80 % ; 20 ml.) was treated during half an hour with zinc dust (1 g.) at 60-70°. The mixture was heated for further 2 hours. The product obtained on working up as before crystallised from acetic acid in needles, m.p. 187°. Mixed m.p. with the product obtained by the condensation of methyl-2,4-dihydroxy-3-methylbenzoate (1.82 g.) with ethyl-α-methyl acetoacetate (1.44 g.) in presence of sulphuric acid (80 % ; 12 ml.) was not depressed.

Analysis :

4.60 mg. of the substance gave 10.83 mg. of carbon dioxide and 2.172 mg. of water.

Found : C = 64.30 % ; H = 5.28 %.

$C_{14}H_{14}O_5$ requires : C = 64.12 % ; H = 5.34 %.

7-Hydroxy-3,4,8-trimethylcoumarin-6-carboxylic acid.

The above ester (0.5 g.) was heated on a steam bath for one hour with sodium hydroxide solution (10 % ; 10 ml.). The mixture was then cooled and acidified. The separated product was purified through sodium bicarbonate solution. It crystallised from dilute acetic acid in needles, m.p.280° (effer.).

Analysis :

9.16 mg. of the substance gave 21.08 mg. of carbon dioxide and 3.78 mg. of water.

Found : C = 62.80 % ; H = 4.62 %.

$C_{13}H_{12}O_5$ requires : C = 62.90 % ; H = 4.83 %.

7-Hydroxy-3,4,8-trimethylcoumarin.

The above acid (0.5 g.) in quinoline (5 ml.) was heated at 200° in an oil bath with a speck of copper powder till effervescence ceased. The mixture was then filtered and poured in dilute hydrochloric acid solution. The separated product crystallised from rectified spirit in needles, m.p.274°. Mixed melting point with the compound obtained on Pechmann condensation of 2-methylresorcinol with ethyl-α-methyl acetoacetate described earlier was not depressed.

Methyl-7-hydroxy-3,8-dicyanomethyl-4-methylcoumarin-6-carboxylate.

Aqueous potassium cyanide (1 g. in 5 ml. water) was slowly added to a suspension of methyl-7-hydroxy-3,8-dichloromethyl-4-methylcoumarin-6-carboxylate (1 g.) in alcohol (25 ml.) and the mixture refluxed on a water bath for one hour. The product obtained on dilution with water and acidification was washed with sodium bicarbonate and then crystallised from acetic acid in needles,m.p.232°.

Analysis :

9.46 mg. of the substance gave 21.26 mg. of carbon dioxide and 3.02 mg. of water.

7.56 mg. of the same substance gave 0.605 ml. of nitrogen at $t = 32°C$ and $p = 757$ mm.

Found : C = 61.31 % ; H = 3.57 % ; N = 8.92 %.

$C_{16}H_{12}O_5N_2$ requires : C = 61.54 % ; H = 3.87 % ; N = 8.97 %.

Attempted Sommelet reaction on methyl-7-hydroxy-3,8-dichloromethyl-4-methylcoumarin-6-carboxylate.

Methyl-7-hydroxy-3,8-dichloromethyl-4-methylcoumarin-6-carboxylate (0.5 g.) in chloroform (40 ml.) was treated with dry hexamine (2.4 g.) andt the solution refluxed on a water bath for 2 hours. A large amount of complex salt separated . It was filtered and boiled for half an hour with dilute acetic acid (1:1 ; 20 ml.). No definite product was obtained on dilution or ether extraction of the above solution.

Chloromethylation of 7-hydroxy-4-methylcoumarin-6-carboxylic acid.

7-Hydroxy-3,8-dichloromethyl-4-methylcoumarin-6-carboxylic acid. A mixture of 7-hydroxy-4-methylcoumarin-6-carboxylic acid (2.2 g. ; 0.01 mole) suspended in glacial acetic acid (50 ml.), paraformaldehyde (4.8 g. ; 0.16 mole) and anhydrous zinc chloride (4.1 g. ; 0.03 mole) was heated at 100° while a current of dry hydrochloric acid gas was passed through it for one hour. The product which separated on cooling crystallised from glacial acetic acid in colourless cubic crystals. It decomposed at 214° but did not give a clear melt. Yield 2.0 g.

Analysis :

9.32 mg. of the substance gave 16.97 mg. of carbon dioxide and 2.59 mg. of water.

17.27 mg. of the same substance gave 15.47 mg. of silver chloride.

Found : C = 49.70 % ; H = 3.12 % ; Cl = 22.16 %.

$C_{13}H_{10}O_5Cl_2$ requires : C = 49.21 % ; H = 3.15 % ; Cl = 22.39 %.

The dimethoxymethyl derivative was prepared by refluxing the above chloromethylcoumarin (0.5 g.) in methyl alcohol (50 ml.) with concentrated sulphuric acid (5 ml.) for 6 hours. The product obtained on diluting the reaction mixture crystallised from rectified spirit in needles, m.p. 138°. Mixed m.p. with methyl-7-hydroxy-3,8-dimethoxymethyl-4-methylcoumarin-6-carboxylate, described earlier, was not depressed.

7-Hydroxy-3,4,8-trimethylcoumarin-6-carboxylic acid.

The above dichloromethyl coumarin (0.5 g.) was reduced by heating its solution in acetic acid (80 % ; 40 ml.) with zinc dust (1 g.) at 60-70° for 2 hours. The product obtained on working up as usual crystallised from acetic acid in needles, m.p. 280° (effer.). Mixed m.p. with 7-hydroxy-3,4,8-trimethylcoumarin-6-carboxylic acid, described earlier, was not depressed.

Chloromethylation of methyl-7-methoxy-4-methylcoumarin-6-carboxylate.

7-Methoxy-3-chloromethyl-4-methylcoumarin-6-carboxylic acid : A mixture of methyl-7-methoxy-4-methylcoumarin-6-carboxylate (2.48 g.; 0.01 mole) in glacial acetic acid (40 ml.), paraformaldehyde (2.4 g. ; 0.08 mole) and anhydrous zinc chloride (4.1 g. ; 0.03 mole) was treated with hydrochloric acid gas at 100° for one hour. On cooling the reaction mixture a crystalline product separated. It crystallised from benzene in colourless needles, m.p. 188-190°. Yield 1.2 g.

Analysis :

4.262 mg. of the substance gave 8.690 mg. of carbon dioxide and 1.528 mg. of water.

9.444 mg. of the same substance gave 4.606 mg. of silver chloride.

Found : C = 55.64 % ; H = 4.01 % ; Cl = 12.07 %.

$C_{13}H_{11}O_5Cl$ requires : C = 55.22 % ; H = 3.88 % ; Cl = 12.56 %.

The methoxymethylcoumarin derivative was prepared by refluxing its solution in methyl alcohol with concentrated sulphuric acid for 10 hours. Esterification took place simultaniously. The product crystallised from rectified spirit in needles,m.p.175°.

Analysis :

8.92 mg. of the substance gave 20.16 mg. of carbon dioxide and 4.38 mg. of water.

Found : C = 61.67 % ; H = 5.49 %.

$C_{15}H_{16}O_6$ requires : C = 61.64 % ; H = 5.52 %.

7-Methoxy-3,4-dimethylcoumarin-6-carboxylic acid.

The above chloromethylcoumarin (0.5 g.) in acetic acid (80 % ; 20 ml.) was reduced by heating with zinc dust (1 g.) at 60-70° for 2 hours. The product obtained on pouring the reaction mixture in cold dilute hydrochloric acid crystallised from acetic acid in needles, m.p.248° (effer.).

Analysis :

9.12 mg. of the substance gave 21.02 mg. of carbon dioxide and 3.68 mg. of water.

Found : C = 62.88 % ; H = 4.51 %.

$C_{13}H_{12}O_5$ requires : C = 62.90 % ; H = 4.87 %.

The same product was obtained when methyl-7-methoxy-3,4-dimethylcoumarin-6-carboxylate (0.5 g.), prepared according to the method of Sethna and Shah

(loc.cit.), was refluxed with alcoholic potassium hydroxide solution (10% ; 20 ml.) for one hour.

Chloromethylation of methyl-5-hydroxy-4-methylcoumarin-6-carboxylate.

Methyl-5-hydroxy-8-chloromethyl-4-methylcoumarin-6-carboxylate : A mixture of methyl-5-hydroxy-4-methylcoumarin-6-carboxylate (4.68 g. ; 0.02 mole) in glacial acetic acid (40 ml.), paraformaldehyde (0.72 g. ; 0.024 mole) and anhydrous zinc chloride (4.1 g.; 0.03 mole) was treated with hydrochloric acid gas at 100° for 2 hours. The product which separated on cooling the reaction mixture was filtered and washed with alcohol. It crystallised from benzene in fine colourless needles,m.p.215-217°. Yield 0.5 g.

Analysis :

8.82 mg. of the substance gave 17.84 mg. of carbon dioxide and 2.96 mg. of water.

14.07 mg. of the same substance gave 7.02 mg. of silver chloride.

Found : C = 55.20 % ; H = 3.75 % ; Cl = 12.66 %.

$C_{13}H_{11}O_5Cl$ requires : C = 55.22 % ; H = 3.88 % ; Cl = 12.56 %.

Methyl-5-hydroxy-4,8-dimethylcoumarin-6-carboxylate.

The above chloromethyl coumarin (0.5 g.,) was reduced by heating its solution in acetic acid (80 % ; 20 ml.) with zinc dust (1 g.) at 60-70° for 2 hours. The product which separated on working up the reaction mixture as before was refluxed with benzene (10 ml.). The insoluble portion crystallised from dilute acetic acid in colourless shining needles,m.p.229°.

Analysis :

9.80 mg. of the substance gave 22.52 mg. of carbon dioxide and 4.10 mg. of water.

Found : C = 62.71 % ; H = 4.68 %.

$C_{13}H_{12}O_5$ requires : C = 62.90 % ; H = 4.87 %.

Pechmann condensation of methyl-2,4-dihydroxy-5-methylbenzoate with ethyl acetoacetate.

2,4-Dihydroxy-5-methylbenzoic acid.

A mixture of 4-methylresorcinol (10 g.),potassium bicarbonate (50 g.) and water (100 ml.) was first heated on a steam bath for 5 hours and then heated vigorously on a wire gauze for half an hour. The mixture was then cooled and acidified with concentrated hydrochloric acid. The separated product was purified through sodium bicarbonate solution. It crystallised from hot water in shining yellow needles,m.p. 212° (effer.). Yield 4.5 g.

Analysis :

8.82 mg. of the substance gave 18.48 mg. of carbon dioxide and 3.76 mg. of water.

Found : C = 57.18 % ; H = 4.77 %.

$C_8H_8O_4$ requires : C = 57.14 % ; H = 4.80 %.

Methyl-2,4-dihydroxy-5-methylbenzoate.

A mixture of the above acid (10 g.) in methyl alcohol (50 ml.) was heated on a steam bath for 10 hours with concentrated sulphuric acid (5 ml.). Excess of methyl alcohol was then removed by distillation and the mixture diluted with large volume of water. The separated product crystallised from benzene-petroleum ether mixture in needles, m.p.122-124°. Yield 8.0 g.

Analysis :

9.12 mg. of the substance gave 19.76 mg. of carbon dioxide and 4.50 mg. of water.

Found : C = 59.13 % ; H = 5.52 %.

$C_9H_{10}O_4$ requires : C = 59.33 % ; H = 5.53 %.

Methyl-5-hydroxy-4,8-dimethylcoumarin-6-carboxylate.

A mixture of methyl-2,4-dihydroxy-5-methylbenzoate (1.82 g.) and ethyl acetoacetate (1.30 g.) was treated with sulphuric acid (80 % ; 10 ml.) and the mixture left overnight at room temperature. Next day the mixture was poured in cold water. The separated solid was filtered and washed with plenty of water. The residue was then treated with saturated solution of sodium bicarbonate and filtered and the residue washed with water. It crystallised from rectified spirit,in needles,m.p.229°. Mixed m.p. with the product obtained on reduction of methyl-5-hydroxy-8-chloromethyl-4-methylcoumarin-6-carboxylate, described earlier, was not depressed.

Condensation of methyl-β-resorcylate with ethyl-α-methyl acetoacetate in presence of anhydrous aluminium chloride : Methyl-7-hydroxy-and methyl-5-hydroxy-3,4-dimethylcoumarin-6-carboxylate.

Anhydrous methyl-β-resorcylate (16.8 g. ; 0.1 mole) and ethyl-α-methyl acetoacetate (15.8 g. ; 0.11 mole) were dissolved in hot dry nitrobenzene (20 ml.) and a solution of anhydrous aluminium chloride (32 g. ; 0.2 mole) in nitrobenzene (120 ml.) added. The mixture protected from mois~~ut~~ture was heated at 125-130° for one hour until the evolution of hydrochloric acid gas was negligible. It was then cooled and ice and hydrochloric acid (10 ml.) added and the nitrobenzene distilled in steam. The brown residue (4.0 g.) was collected and dissolved completely in hot rectified spirit and the solution allowed to cool.

The separated product crystallised from rectified spirit in needles, m.p. 214°. Mixed m.p. with methyl-7-hydroxy-3,4-dimethylcoumarin-6-carboxylate prepared by the Pechmann condensation of methyl-β-resorcylate with ethyl-α-methyl acetoacetate in presence of sulphuric acid according to the method of Sethna and Shah (loc.cit.) was not depressed.

The substance obtained after diluting the original alcoholic filtrate with water crystallised from dilute acetic acid in needles, m.p. 191°. Yield 0.4 g. Mixed m.p. with methyl-7-hydroxy-3,4-dimethylcoumarin-6-carboxylate was depressed by over 20°.

It forms a yellow sodium salt with 10% sodium hydroxide.

Analysis :

10.20 mg. of the substance gave 23.42 mg. of carbon dioxide and 4.50 mg. of water.

Found : C = 62.66 % ; H = 4.94 %.

$C_{13}H_{12}O_5$ requires : C = 62.90 % ; H = 4.87 %.

Methyl-5-hydroxy-3,8-dichloromethyl-4-methylcoumarin-6-carboxylate.

A mixture of methyl-5-hydroxy-4-methylcoumarin-6-carboxylate (2.34 g. ; 0.01 mole) in glacial acetic acid (60 ml.), paraformaldehyde (4.8 g. ; 0.16 mole) and anhydrous zinc chloride (4.1 g. ; 0.03 mole) was treated with hydrochloric acid gas at 100° for one hour. On cooling the reaction mixture a crystalline product separated. It was filtered washed with alcohol and dried. It crystallised from benzene in needles, m.p. 168°. Yield 2.2 g.

Analysis :

9.54 mg. of the substance gave 17.72 mg. of carbon dioxide and 3.06 mg. of water.

9.834 mg. of the same substance gave 8.396 mg. of silver chloride.

Found : C = 50.70 % ; H = 3.58 % ; Cl = 21.13 %.

$C_{14}H_{12}O_5Cl_2$ requires : C = 50.75 % ; H = 3.62 % ; Cl = 21.45 %.

The diacetoxymethyl derivative prepared as before was crystallised from rectified spirit in needles, m.p. 125-127°.

Analysis :

10.42 mg. of the substance gave 21.84 mg. of carbon dioxide and 4.52 mg. of water.

Found : C = 57.20 % ; H = 4.85 %.

$C_{18}H_{18}O_9$ requires : C = 57.14 % ; H = 4.76 %.

The dimethoxymethyl derivative prepared as before crystallised from rectified spirit in needles,m.p.144°.

Analysis :

9.82 mg. of the substance gave 21.42 mg. of carbon dioxide and 4.82 mg. of water.

Found : C = 59.53 % ; H = 5.49 %.

$C_{16}H_{18}O_7$ requires : C = 59.62 % ; H = 5.59 %.

Methyl-5-hydroxy-3,4,8-trimethylcoumarin-6-carboxylate.

The above 3,8-dichloromethylcoumarin (1 g.) was reduced by heating its acetic acid solution (80 % ; 40 ml.) with zinc dust (2 g.) at 60-70° for two hours. The product obtained on working up the reaction mixture as before was boiled with benzene (5 ml.) for 5 minutes and filtered. The insoluble portion crystallised from acetic acid in shining needles,m.p.218°.

Analysis :

9.16 mg. of the substance gave 21.54 mg. of carbon dioxide and 4.36 mg. of water.

Found : C = 64.16 % ; H = 5.32 %.

$C_{14}H_{14}O_5$ requires : C = 64.12 % ; H = 5.34 %.

5-Hydroxy-3,4,8-trimethylcoumarin-6-carboxylic acid.

The above ester (0.5 g.) was heated on a steam bath for one hour with sodium hydroxide solution (10 % ; 10 ml.). The mixture was then cooled and acidified with dilute hydrochloric acid. The separated product was purified through sodium bicarbonate treatment. It crystallised from dilute acetic acid in needles, m.p. 274° (effer.).

Analysis :

9.18 mg. of the substance gave 21.14 mg. of carbon dioxide and 3.82 mg. of water.

Found : C = 62.84 % ; H = 4.66 %.

$C_{13}H_{12}O_5$ requires : C = 62.90 % ; H = 4.83 %.

5-Hydroxy-3,4,8-trimethylcoumarin.

The above acid (0.5 g.) in quinoline (10 ml.) was refluxed on a sand bath for 1/2 hour with a speck of copper powder. The mixture was then filtered and poured in dilute hydrochloric acid solution. The separated product crystallised from rectified spirit in needles, m.p. 246°.

Analysis :

7.98 mg. of the substance gave 20.48 mg. of carbon dioxide and 4.02 mg. of water.

Found : C = 70.04 % ; H = 5.64 %.

$C_{12}H_{12}O_3$ requires : C = 70.58 % ; H = 5.88 %.

5-Methoxy-3,4,8-trimethylcoumarin.

The above coumarin was methylated in acetone solution with dimethyl sulphate in presence of anhydrous potassium carbonate as before. It crystallised from dilute acetic acid in colourless needles, m.p. 198°.

Analysis :

9.04 mg. of the substance gave 23.60 mg. of carbon dioxide and 5.14 mg. of water.

Found : c = 71.23 % ; H = 6.36 %.

$C_{13}H_{14}O_3$ requires : c = 71.55 % ; H = 6.42 %.

Chloromethylation of 5-methoxy-4-methylcoumarin :

?,?'-Methylene bis- (5-methoxy-4-methylcoumarin)

A suspension of 5-methoxy-4-methylcoumarin (1.9 g. ; 0.01 mole) in water (50 ml.) and paraformaldehyde (0.3 g. ; 0.01 mole) was treated with hydrochloric acid gas at 60-70° for 1 hour. The separated product was filtered. It crystallised from glacial acetic acid in colourless silky needles, m.p. 268°.

Analysis :

9.62 mg. of the substance gave 24.78 mg. of carbon dioxide and 4.72 mg. of water.

Found : C = 70.29 % ; H = 5.49 % .

$C_{23}H_{20}O_6$ requires : C = 70.40 % ; H = 5.10 % .

5-Methoxy-3,8-dichloromethyl-4-methylcoumarin

A mixture of 5-methoxy-4-methylcoumarin (1.9 g. ; 0.01 mole) in acetic acid (80 % ; 40 ml.) and paraformaldehyde (2.4 g. ; 0.08 mole) was treated with hydrochloric acid gas at 60-70° for 3 hours and the mixture left over-night. The next day the separated solid was filtered and dried. It crystallised from benzene in needles, m.p. 173-75°. Yield 0.8 g.

Analysis :

8.32 mg. of the substance gave 16.44 mg. of carbon dioxide and 3.04 mg. of water.

18.24 mg. of the substance gave 18.12 mg. of silver chloride.

Found : C = 53.93 % ; H = 4.08 % ; Cl = 24.58 %.

$C_{13}H_{12}O_3Cl_2$ requires : C = 54.35 % ; H = 4.18 % ; Cl = 24.73 %.

The diacetoxymethyl derivative prepared as before crystallised from rectified spirit in needles, m.p. 168-70°.

Analysis :

10.04 mg. of the substance gave 22.46 mg. of carbon dioxide and 4.68 mg. of water.

Found : C = 61.03 % ; H = 5.21 %.

$C_{17}H_{18}O_7$ requires : C = 61.07 % ; H = 5.43 %.

5-Methoxy-3,4,8-trimethylcoumarin

The above dichloromethylcoumarin (0.5 g.) was reduced by heating its solution in acetic acid (80 % ; 20 ml.) with zinc dust (1 g.) at 60-70° for 2 hours. The product obtained on working up as usual crystallised from rectified spirit in needles, m.p. 198°. Mixed m.p. with 5-methoxy-3,4,8-trimethylcoumarin, mentioned earlier, was not depressed.