

AN APPROACH TO THE SYNTHESIS OF AVICENNIN

by

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Chung Chi College

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SUMMARY

The synthesis of avicennin, a natural product isolated from a local plant, was attempted. A modified synthetic scheme of A. Robertson was employed in the synthesis of the basic skeleton. Phloroglucinol was reacted with 3,3-dimethylacrylic acid in the presence of zinc chloride and phosphorus oxychloride to produce 5,7-dihydroxy-2,2-dimethylchroman-4-one (XIV). Benzoylation and methylation of (XIV) gave 7-benzyloxy-5-methoxy-2,2-dimethylchroman-4-one (XCI) which in turn was debenzylated by means of hydrogenolysis to produce the 7-hydroxy-5-methoxy derivative (LII). Clemmensen reduction of (LII) gave no crystallizable product. Lithium aluminium hydride reduction gave 7-hydroxy-5-methoxy-2,2-dimethylchroman-4-ol (XCVI). Dehydration of (XCVI) did not produce the required chromene. Another blocking group, the *p*-tolylsulfonyloxy group was employed instead, and after methylation, reduction, dehydration, and then removal of the blocking group, 7-hydroxy-5-methoxy-2,2-dimethylchromene (XCVII) was obtained. Condensation of chromene with malic acid did not produce the expected product: alloxanthoxyletin. Condensation of 5,7-dihydroxy-2,2-dimethylchroman-4-one (XIV) with malic acid yielded the correct angular isomer (LXXXV) leading to alloxanthoxyletin. After methylation, the reduction with sodium borohydride has not yet been successfully carried out.

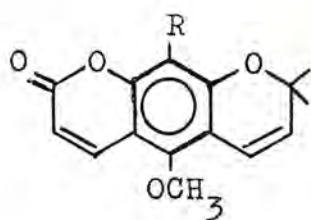
The introduction of the side chain has not been attempted and the complete synthesis of avicennin was still an unfinished task.

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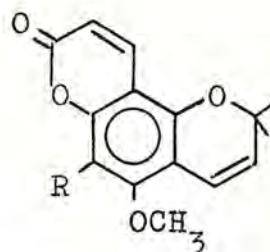
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I. INTRODUCTION

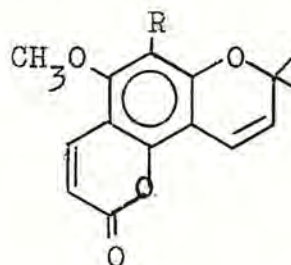
Avicennin, a chromeno- α -pyrone derivative, was first isolated by H. R. Arthur¹ from the root-bark and the bark of Zanthoxylum avicennae in 1957. It was later also found in Erios-temon coccineus.² Basing on the elemental analysis, this yellow compound, in the form of elongated prisms, m. p. 141-142^o, was believed to have the molecular formula of C₂₀H₂₂O₄. From the results of oxidation of avicennin, its hydrolytic fission, its ozonolysis, and catalytic hydrogenation reactions, three possible structures (I a-c) each with an isopentenyl group as side chain were first proposed by Arthur in 1957,¹ and again in 1960.³ Later in 1963, through the examination of the nuclear magnetic resonance spectrum of avicennin, the molecular formula was revised to be C₂₀H₂₀O₄. Consequently the structures were revised (II a-c) by Arthur and Ollis⁴ that the side chain should be a β -methyl-trans-butadienyl group instead of the previous proposed one. However, the definite structure for avicennin could not be established yet.



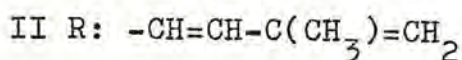
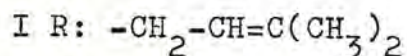
(I, II a)



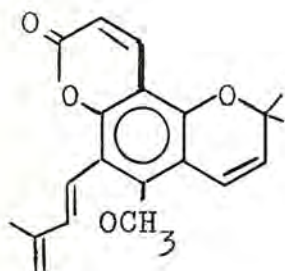
(I, II b)



(I, II c)

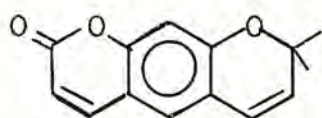


Until 1969, T. F. Lai⁵ succeeded by using X-ray crystallography to establish the final structure of avicennin (IIb), which is identical with one of the three possible structures originally proposed by Arthur and Ollis.⁴

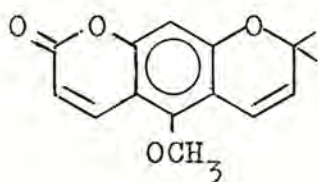


(IIb)

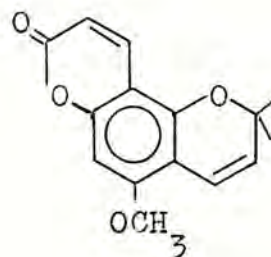
Chromeno- α -pyrones of this type have been isolated previously: xanthyletin (III), xanthoxyletin (IV), and alloxanthoxyletin (V) from the bark of Xanthoxylum americanum; luvangetin (VI) from Luvunga scandens, and seselin (VII) from Seseli indicum.^{1,6}



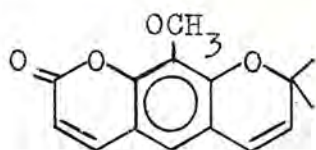
(III)



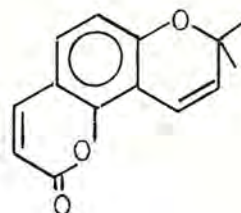
(IV)



(V)



(VI)



(VII)

Although all of these have the tricyclic dimethylchromenocoumarin structures, none of these possesses a 3-methyl-trans-butadienyl side chain. In fact, many natural phenolic compounds contain C₅-residues which are isoprenoid in type,⁷ but this 3-methyl-trans-butadienyl group represents a hitherto unrecognized substituent.⁴

Syntheses of the above compounds have been carried out with some success.^{6,8} The syntheses of alloxanthoxyletin and dihydroalloxanthoxyletin⁹ were of particular interest, since alloxanthoxyletin (V) has a similar structure as avicennin (IIb) except that the 3-methyl-trans-butadienyl side chain was absent.

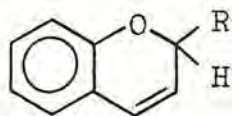
The synthesis of avicennin has not been attempted before, except for the partial attempt to introduce the isopentenyl side chain into the naturally occurring xanthoxyletin nucleus (IV) to form the structure (Ia).¹⁰ The synthesis of avicennin was carried out with the hope that it may supply a further proof for the structure of this natural product, and also that a general synthetic scheme for the chromeno- α -pyrone system may be obtained.

II. HISTORICAL REVIEW

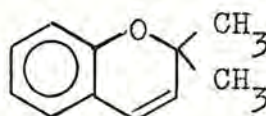
Avicennin (IIb) is a tricyclic compound whose basic structure is made up of a chromene ring and a coumarin ring. When trying to tackle the synthetic problem of avicennin, there are four main topics that have to be discussed, namely, the chromene ring synthesis, the selective methylation, the coumarin ring formation and the side chain introduction. Followings are discussions of each of these topics in some detail, and a brief account of the synthesis of the chromeno- α -pyrone systems.

A. Chromene Ring Synthesis

There are various methods to synthesize chromene (VIIIa) which is monosubstituted at the 2-position,¹¹ but since only the 2,2-dimethylchromene system (VIIIb) is present in avicennin (IIb), only the synthetic methods leading to the production of this structure (VIIIb) will be reviewed.



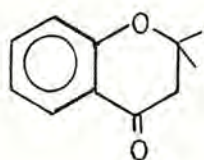
(VIIIa)



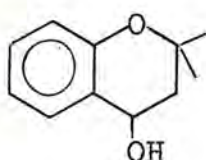
(VIIIb)

The most commonly employed method for the synthesis of 2,2-dimethylchromene is via the reduction of the carbonyl group

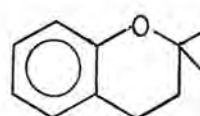
of 2,2-dimethylchroman-4-one (IX) to form 2,2-dimethylchroman-4-ol (X), which upon dehydration gives the corresponding chromene (VIIIb). The chroman-4-one (IX) may also be reduced to form chromane (XI) which undergoes dehydrogenation to produce the chromene (VIIIb).



(IX)



(X)



(XI)

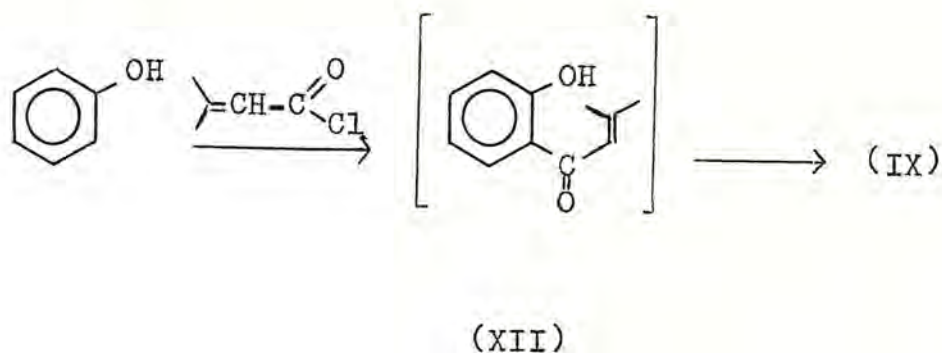
The 2,2-dimethylchromene system (VIIIb) may also be formed directly from phenol or its derivatives by employing 3-methylbut-2-enal and its derivatives. Through the Grignard addition, by using methyl magnesium iodide, to coumarins, again chromene (VIIIb) may be obtained.

Each of the above methods will be dealt with in some detail.

(1) From Chroman-4-ones

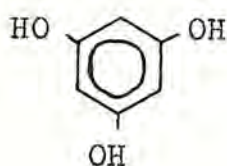
Synthesis of Chroman-4-ones:

2,2-Dimethylchroman-4-one (IX) may be obtained through the Friedel-Crafts acylation reaction with phenols. By condensing 3,3-dimethylacrylic chloride, its acid, or its β -halo derivative with phenol or its derivatives, the corresponding 2,2-dimethylchroman-4-one (IX) may be formed.¹² It was believed that the chalcone (XII) was the intermediate, which underwent cyclization to produce the final product.¹³ The common Lewis acids employed in this condensation are aluminium chloride, zinc chloride, antimony trichloride, boron trifluoride, or polyphosphoric acid. It was also reported that the chalcone (XII) may be cyclized in the presence of dilute bases or acids.¹² Bases which induce cyclization are dilute sodium hydroxide or sodium acetate. Acids that have been used are dilute hydrochloric acids, aqueous alcoholic sulfuric acid, or phosphoric acids.

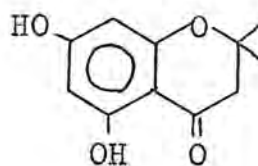


5,7-Dihydroxy-2,2-dimethylchroman-4-one (XIV) is of

particular interest since it provides a suitable entry for the synthesis of avicennin. Phloroglucinol (XIII) was used as starting material, and by employing aluminium chloride as Lewis acid, 3,3-dimethylacrylic chloride as acylating agent, and nitrobenzene as solvent, A. Robertson and his co-workers¹⁴ succeeded in preparing the required chroman-4-one (XIV) with a 50% crude yield. The same method was employed by J. Polonsky¹⁵ and later by A. K. Ganguly and his co-workers⁸ in the synthesis of some chromeno- α -pyrone derivatives.



(XIII)



(XIV)

M. Miyano and M. Matsui¹⁶ introduced some new condensing agents for the preparation of chroman-4-ones. By using antimony trichloride and 3,3-dimethylacrylic acid with phloroglucinol (XIII), a maximum yield of 30% was obtained. Zinc chloride or stannous chloride proved to be less reactive. Later M. Nakayima and his co-workers¹⁷ employed boron trifluoride as catalyst successfully. H. B. Bhat and K. Venkataraman¹⁸ also reported a general method for the synthesis of 2,2-dimethylchroman-4-ones by using boron trifluoride in ether as condensing agent, and 3,3-dimethyl-3-hydroxyacrylic acid as acylating agent. A 67% yield of

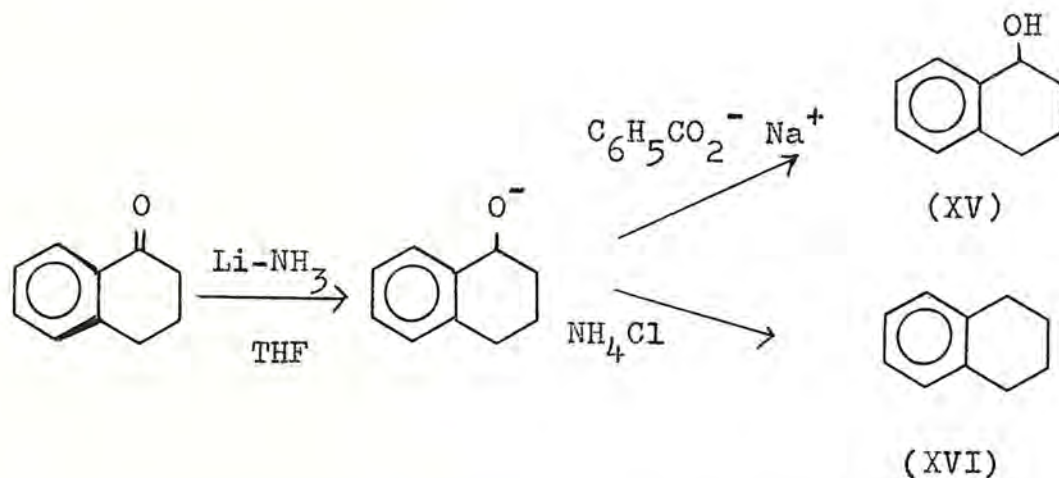
5,7-dihydroxychroman-4-one (XIV) was obtained. Polyphosphoric acid was employed as a condensing agent by P. S. Bramwell and his co-workers¹⁹ in reacting 3,3-dimethylacrylic acid with phloroglucinol (XIII). Quite recently P. R. Iyer and G. D. Shah²⁰ reported the usage of zinc chloride-phosphorus oxychloride reagent as the condensing agent, and a 67% yield of (XIV) was obtained.

Reduction of the Carbonyl Group:

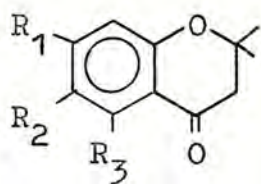
Reduction of the carbonyl groups to form alcohols and to form methylene derivatives has been well studied. These reductions may be accomplished by employing metals, metallic hydrides and alkoxides, diborane and its derivatives, through catalytic hydrogenation, and also the Wolff-Kishner reaction. Under different conditions, either the alcohol or the methylene derivatives are obtained.

Ketones may be successfully reduced with lithium or sodium, either as the free metal or as solutions in liquid ammonia or in alcohols.²¹ Recently it was reported that in the reduction of aromatic ketones by lithium in liquid ammonia with tetrahydrofuran (THF) as solvent, in the presence of sodium benzoate, the corresponding alcohol (XV) was obtained. However, for the same reduction but in the presence of ammonium chloride, the methylene derivative (XVI) was formed. This result was believed to be due to the fact that ammonium chloride was able to protonate the intermediate which underwent

further reduction to produce the hydrocarbon (XVI).²²

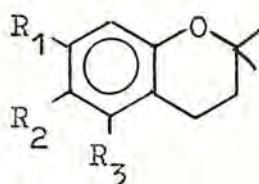


Clemmensen reduction²³ of ketones with zinc amalgam in strong aqueous acids can reduce chroman-4-ones into chromanes,²⁴ and this method was used by G. H. Stout and K. L. Stevens²⁵ in reducing 7-methoxy-5-hydroxychroman-4-one (XVIIa) and by H. B. Bhat¹⁸ in reducing 6,7-dimethoxychroman-4-one (XVIIb) to form the corresponding chromanes (XVIII a,b).



(XVII)

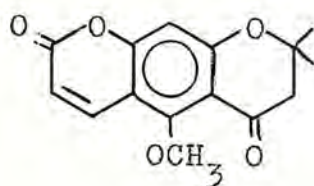
- a. R_1 : $-\text{OCH}_3$
 R_2 : $-\text{H}$
 R_3 : $-\text{OH}$



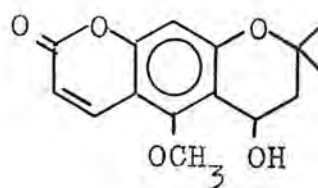
(XVIII)

- b. R_1 : $-\text{OCH}_3$
 R_2 : $-\text{OCH}_3$
 R_3 : $-\text{H}$

The most common metallic hydride employed in reduction is lithium aluminium hydride.^{26,27} Sodium borohydride is also often used,²⁸ but its reactivity is lower than that of lithium aluminium hydride. This property rendered sodium borohydride to have better selectivity in reducing functional groups.²⁹ Lithium aluminium hydride reduces lactones into diols, while sodium borohydride has no reaction. This property was utilized by A. K. Ganguly and co-workers⁸ in the reduction of the methyl ether of clausenin (XIX) to produce the corresponding alcohol (XX), leaving the lactone ring intact.

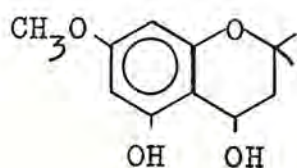


(XIX)

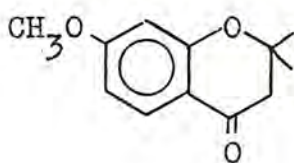


(XX)

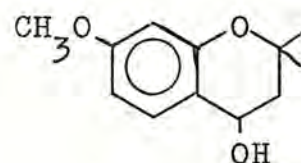
Sodium borohydride has also been employed in the reduction of 7-methoxy-5-hydroxychroman-4-one (XVIIa) to form chroman-4-ol (XXI).²⁵ Lithium aluminium hydride was used by J. R. Beck and co-workers²⁸ to reduce 7-methoxychroman-4-one (XXII) to the corresponding chroman-4-ol (XXIII) with 80% yield.



(XXI)



(XXII)



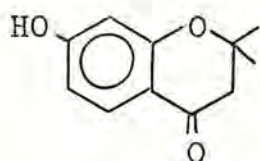
(XXIII)

In the presence of aluminium chloride, both lithium aluminium hydride and sodium borohydride may produce the methylene derivative instead of alcohol.³⁰ It was reported that 7-methoxy-5-hydroxychromane (XVIIIa) was obtained by using sodium borohydride in aqueous methanol with dilute hydrochloric acid.²⁵

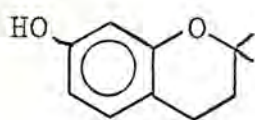
Metallic alkoxides commonly employed in reduction are aluminium ethoxide and aluminium isopropoxide. This is the well-known Meerwein-Ponndorf-Verley reaction.³¹ Although there are many examples of reduction of ketones to alcohols in very good yield (70-90%), but none was found for the reduction of chroman-4-one to chroman-4-ol by using aluminium alkoxides.

Diborane has been employed in the reduction of many functional groups,³² and ketones were often reduced to alcohols. Usually the derivatives of diborane were used to ensure greater selectivity.³³ Diborane may also reduce the ketone to form methylene derivative, as reported by H. B. Bhat¹⁸ in the reduction of 6,7-dimethoxychroman-4-one (XVIIb) to form the corresponding chromane (XVIIIb).

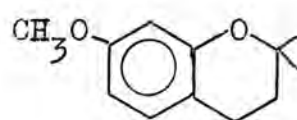
Catalytic hydrogenation of carbonyl groups to form alcohols is usually effected under mild conditions over platinum, the more active forms of Raney nickel, ruthenium and rhodium catalysts on alumina, and palladium.³⁴ It was reported by A. Robertson³⁵ that reduction of 7-hydroxychroman-4-one (XXIV) using palladium-charcoal catalyst under hydrogen, produced a mixture of chromane (XXV) and unchanged chroman-4-one.



(XXIV)

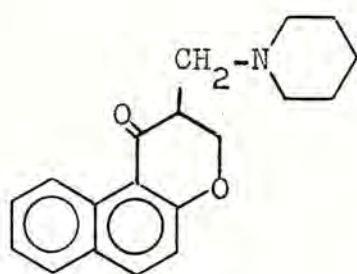


(XXV)

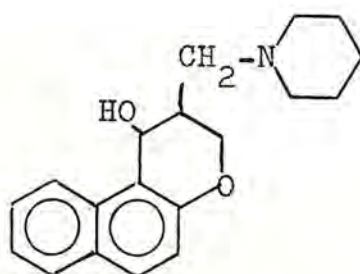


(XXVI)

7-Methoxychroman-4-one (XXII) was reported to undergo reduction in the presence of copper chromite at 200° and under a hydrogen pressure of 300 psi., or with Raney nickel at 50 psi. at room temperature to form the corresponding chromane (XXVI).²⁸ When platinum oxide was used as catalyst, reduction of the chroman-4-one (XXVII) to the chroman-4-ol (XXVIII) resulted.³⁶

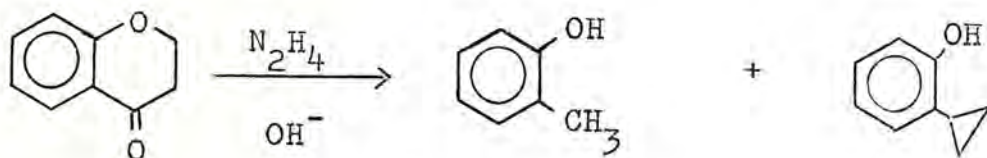


(XXVII)



(XXVIII)

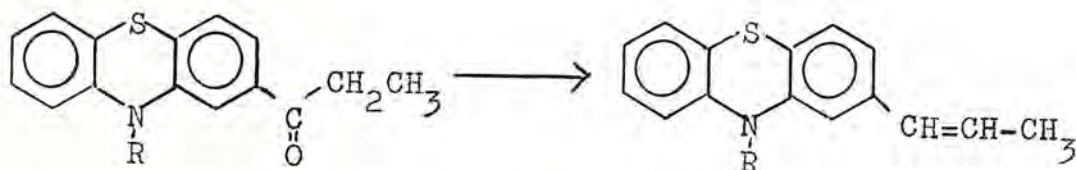
The Wolff-Kishner reaction reduces ketones to methylene derivatives under alkaline conditions.³⁷ This reaction was found to be successful especially for compounds that are sensitive to acids. It was reported by Belinger,³⁷ however, that reduction of chroman-4-one (XXIX) gave 20% o-cresol, and 40% o-cyclopropylphenol (XXX), instead of the expected chromane.



(XXIX)

(XXX)

Carbonyl groups may also be converted to their ethylene derivatives directly. In an anomalous Clemmensen reduction, employing zinc powder, mercuric chloride, and 20% acetic acid, refluxing for 15 hours, with stirring under nitrogen, the ethylene derivative was produced:³⁸

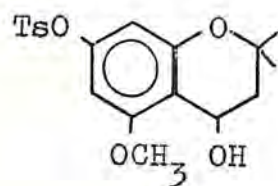


Aluminium isopropoxide also reduced ketones to ethylene derivatives in xylene.³⁹ Recently it was reported that by using lithium in liquid ammonia in *t*-butyl alcohol,⁴⁰ or lithium borohydride in dioxane, in the presence of acetic acid, the same reaction occurred.⁴¹

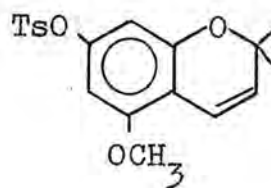
Dehydration Methods:

Dehydration of alcohols may be carried out in the presence of various reagents, and is well documented.⁴² For easi-

ly dehydrated alcohols such as the benzyl alcohol, refluxing the starting material with a trace amount of *p*-toluenesulfonic acid in toluene or benzene, is sufficient to produce the corresponding ethylene derivative. This method was employed in the dehydration of 5-methoxy-7-(*p*-tolylsulfonyloxy)chroman-4-ol (XXXI) to the corresponding chromene (XXXII).²⁷

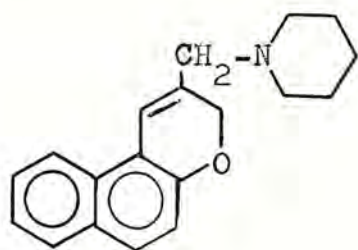


(XXXI)

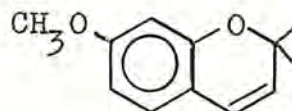


(XXXII)

The secondary alcohol (XX) of the methyl ether of clausenin (XIX), when mixed intimately with fused KHSO_4 and heated at $90-100^\circ/0.1$ mm. in a sublimation tube, underwent dehydration to produce xanthoxyletin (IV).⁸



(XXXIII)



(XXXIV)

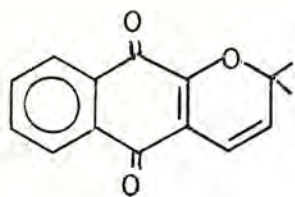
The chroman-4-ol (XXVIII) was dehydrated when 0.01 mole of ethanolic hydrochloric acid was added gradually to a solution of 0.01 mole of chroman-4-ol (XXVIII) in butyl ether to give

the corresponding chromene (XXXIII).³⁶ 7-Methoxychromene (XXXIV) was produced when treating the chroman-4-ol (XXIII) in benzene with phosphorus oxychloride at 85-90°. ²⁸

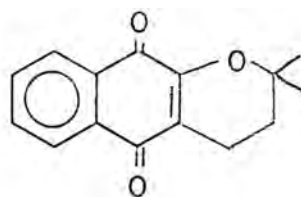
Dehydrogenation Methods:

Dehydrogenation can be effected by heating the alkane in the presence of hydrogenation catalysts, such as platinum or palladium, or easily reducible substances, such as selenium or chloranil.^{43a} Recently it has been reported that pyrolysed polyacrylonitrile can be used as a chemical dehydrogenation agent, which converts cyclohexene to benzene with 50% yield.^{43b}

2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ) has been widely used in dehydrogenation processes. A. R. Burnett and R. H. Thomson^{44a} employed DDQ in the preparation of dehydro- α -lapachone (XXXV) from its dihydro-derivative (XXXVI).

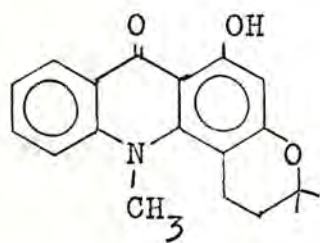


(XXXV)



(XXXVI)

It was also reported that nordihydroacronycine (XXXVII) with DDQ refluxing in toluene produced noracronycine (XXXVIII).²⁸

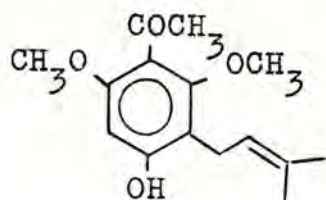


(XXXVII)

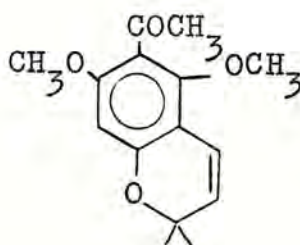


(XXXVIII)

DDQ has also been used in the cyclodehydrogenation of γ , γ -dimethylallylphenol (XXXIX) to produce chromene (XL) directly.^{44b}



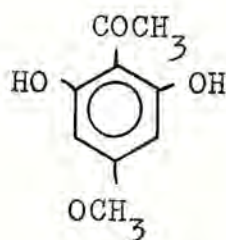
(XXXIX)



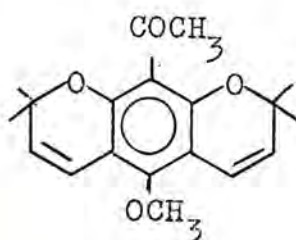
(XL)

(2) Direct Synthesis of Chromenes

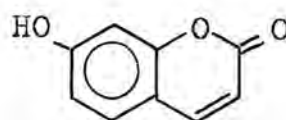
Several dimethylchromenylation reagents were discovered recently. 3-Hydroxy-3-methylbut-1-yne has been used to react with 2,6-dihydroxy-4-methoxyacetophenone (XLI) to produce alloevodionol (XLII).⁴⁵



(XLI)



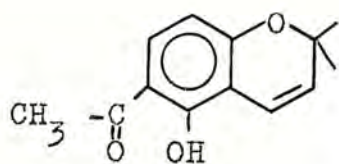
(XLII)



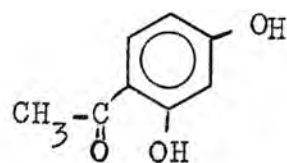
(XLIII)

By refluxing a solution of phenol derivative and 3-chloro-3-methylbut-1-yne in acetone, in the presence of potassium iodide and potassium carbonate, the product thus formed was then rearranged to produce the corresponding chromene in boiling diethylaniline. When umbelliferone (XLIII) was used as the phenol derivative, seselin (VII) was formed.⁴⁶

3-Methylbut-2-enal and its derivatives have been widely used in the preparation of chromenes.⁴⁷ With 3-methylbut-2-enal, W. M. Bandaranayake and co-workers^{47c} succeeded to prepare the corresponding chromene (XLIV) from 2,4-dihydroxyacetophenone (XLV) in 59% yield. When the methyl acetal of this reagent was employed instead, the same product was formed with 60% yield.

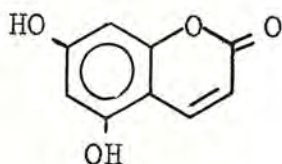


(XLIV)

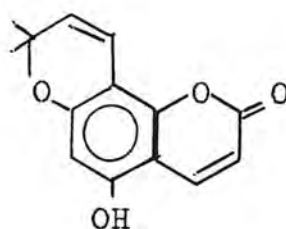


(XLV)

Condensing 5,7-dihydroxy coumarin (XLVI) with 3-hydroxy-3-methyl-1,1-dimethoxybutane, the corresponding chromene (XLVII) was formed with 45% yield.



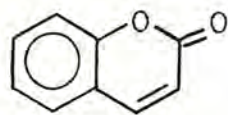
(XLVI)



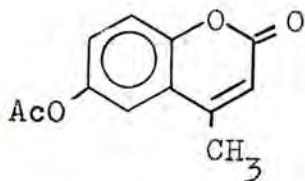
(XLVII)

(3) From Coumarin

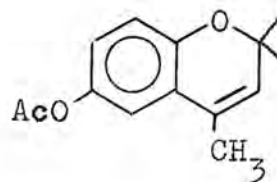
Grignard addition to coumarin has been employed in several cases to produce chromenes. The reaction of methyl magnesium iodide with coumarin (XLVIII) was reported to give the 2,2-dimethylchromene (VIIIb).^{48,49} F. Bergel and A. R. Todd⁵⁰ treated 6-acetoxy-4-methylcoumarin (XLIX) with the same reagent, to give the chromene (L).



(XLVIII)



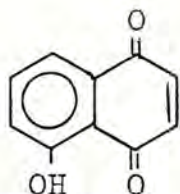
(XLIX)



(L)

B. Selective Methylation

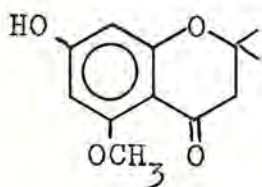
Various reagents may be used for methylating phenols, such as diazomethane, dimethyl sulfate, and methyl iodide.^{12,51} It was reported that diazomethane methylates all phenoxy groups except the 5-OH group in the chroman-4-one. At room temperature, similar results are obtained with methyl sulfate, but at higher temperatures (40-50°), all phenoxy groups are methylated. Methyl iodide and potassium carbonate in acetone may give rise to the methylated chroman-4-one, as reported in the methylation of 5,7-dihydroxychroman-4-one (XIV) to produce 7-methoxy-5-hydroxychroman-4-one (XVIIa).^{24,25} By employing methyl iodide with silver oxide in chloroform, J. F. Garden and R. H. Thomson⁵² succeeded to methylate the chelated peri-hydroxyl group in juglone (LI).



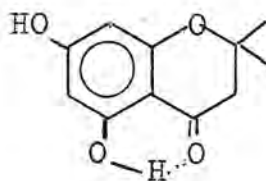
(LI)

A. Robertson⁵³ reported another method of methylation. By saturating a solution of phloroglucinol (XIII) in methyl alcohol with dry hydrogen chloride, the monomethyl ether and the dimethyl ether were obtained.

From the structure of avicennin (IIb), it can be seen that the methoxy group is at the 5-position. If 5,7-dihydroxychroman-4-one (XIV) is used as the starting material, the 7-position must be protected so as to obtain 7-hydroxy-5-methoxychroman-4-one (LII), since it is much more reactive than the 5-hydroxyl group, the latter being chelated to the carbonyl group (LIII). Thus blocking groups has to be employed.⁵⁴

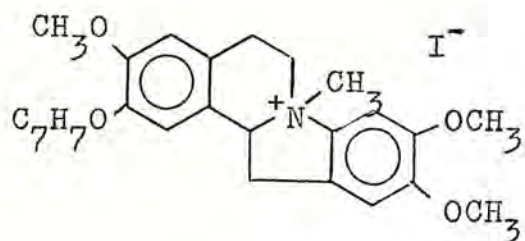


(LII)

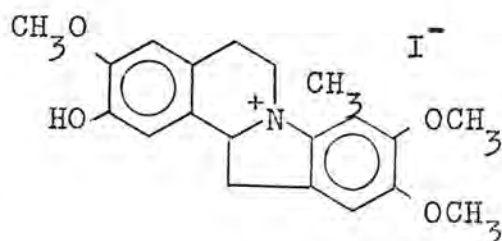


(LIII)

A. Robertson²⁴ used the benzyl group as blocking group in the preparation of 5-methoxy derivative (LII). Debenzylation was effected by hydrogenolysis with 10% palladium on charcoal catalyst. Apart from palladium, nickel or platinum catalysts may also be used, but palladium is preferred if hydrogenation of the nucleus is to be avoided.⁵⁵ There are other chemical methods for debenylation. Trifluoroacetic acid cleaves aromatic benzyl ethers at room temperature.⁵⁶ T. Kametani and K. Ogasawara⁵⁷ used concentrated hydrochloric acid to cleave the benzyl ether (LIV) to form the debenzylated derivative (LV).

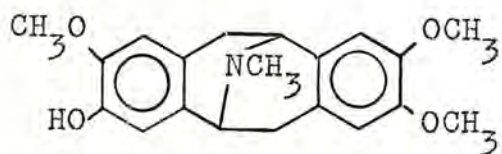


(LIV)

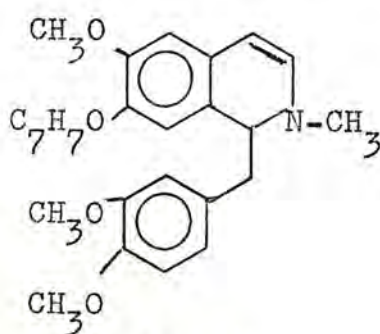


(LV)

By using a mixture of 85.6% phosphoric acid and 90.8% formic acid at 100° , norargemonine (LVI) was formed from its benzyl derivative (LVII) after cyclization.⁵⁸

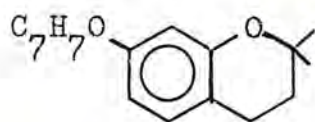


(LVI)

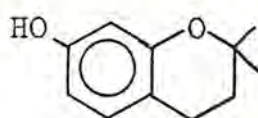


(LVII)

7-Benzyloxymorphane (LVIII) was also debenzylated to form 7-hydroxymorphane (LIX) by refluxing with acetic acid and concentrated hydrochloric acid.³⁵



(LVIII)

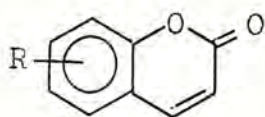


(LIX)

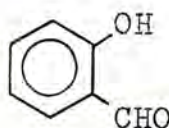
Acetylation⁵⁹ and tolylsulfonation²⁷ are also good blocking reactions, and these protecting groups can be removed easily by alkaline hydrolysis.⁶⁰

C. Coumarin Ring Synthesis

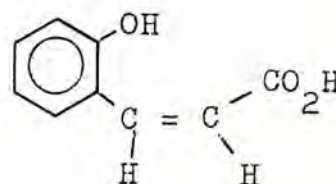
Preparation of coumarins has been widely studied and well documented.^{61,62} Only the unsubstituted pyrone ring is present in avicennin (IIb), so that synthetic methods leading to coumarin (LX) will be reviewed.



(LX)



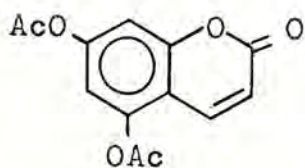
(LXI)



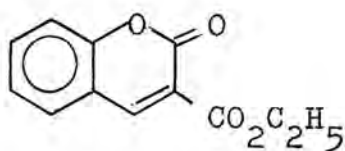
(LXII)

Coumarins may be prepared from salicylaldehydes (LXI). The Perkin reaction⁶³ has proved successful with a number of salicylaldehydes which gives varying yield of coumarin (XLVIII). This condensation was carried out with acetic anhydride in the presence of sodium acetate at temperature around 140°. It was believed that the 2-hydroxycinnamic acid (LXII) first formed, underwent cyclization to produce the product.⁶⁴ When iodine was added as a catalyst for cyclization, a higher yield of coumarin (70%) was obtained.⁶¹ When phloroglucinaldehyde was

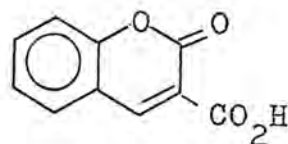
heated with sodium acetate and acetic anhydride, excellent yield of 5,7-diacetoxycoumarin (LXIII) was obtained.⁶⁰



(LXIII)

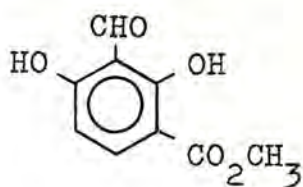


(LXIV)

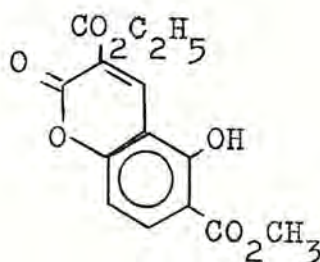


(LXV)

3-Carboxycoumarins (LXIV) can be obtained in good yields by the application of Knoevenagel reaction.^{65,66} By reacting salicylaldehyde with malonic acid or its derivatives in the presence of an organic base, such as pyridine, the coumarin-3-carboxylic acid (LXV) may be obtained after hydrolysis. Decarboxylation of the 3-carboxycoumarin (LXV) may give the unsubstituted pyrone derivative (XLVIII). R. C. Shah⁶⁶ reported that by applying the Knoevenagel reaction to methyl β -resorcylate (LXVI) with ethyl malonate, in the presence of piperidine, the corresponding 3-carboxycoumarin (LXVII) was formed.



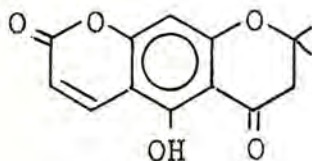
(LXVI)



(LXVII)

Coumarins may also be prepared from phenols. The v. Pechmann condensation is the most important method for preparing coumarins since it proceeds from very simple starting materials, and gives good yields of coumarins.⁶¹ By employing malic acid in the presence of a condensing agent, the coumarin (LX) may be obtained from phenol and its derivatives. The commonly used condensing agents are concentrated sulfuric acid, 73% sulfuric acid, hydrogen chloride in acetic acid or in alcohol, zinc chloride, phosphoric acid, sodium ethoxide, boric anhydride, sodium acetate, phosphorus oxychloride, phosphorus pentoxide and aluminium chloride. Besides malic acid, fumaric acid and maleic acid may be employed. Resorcinol reacted with malic acid in concentrated sulfuric acid at 120° to produce umbelliferone (XLIII) in 43% yield.⁶⁷

The acid catalysed condensation of ethyl propiolate with reactive phenols appears to be an effective method for the preparation of 3,4-unsubstituted coumarins (LX). K. D. Kaufman and R. C. Kelly⁶⁸ reported that 5,7-dihydroxycoumarin (XLVI) was formed with 89% yield from the condensation of phloroglucinol with ethyl propiolate in the presence of zinc chloride. This reaction was also employed by A. K. Ganguly⁸ in the preparation of clausenin (LXVII) from 5,7-dihydroxychroman-4-one (XIV).



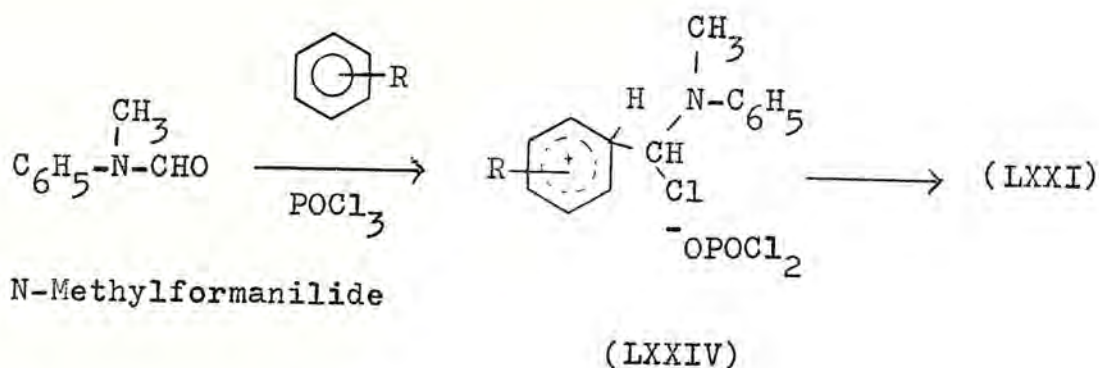
(LXVIII)

D. Introduction of Side Chain

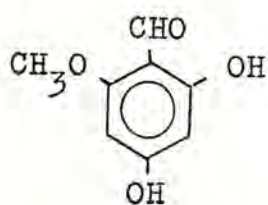
The side chain present in avicennin (IIb) is the 3-methyl-trans-butadienyl group, which has a double bond directly conjugated to the aromatic ring. The best method for the introduction of such a double bond is by the Wittig reaction.⁶⁹ The Wittig reaction is a very useful synthetic method for the preparation of olefins. The reaction of a tertiary phosphine (usually triphenylphosphine) with an alkyl halide, alkenyl halide or other derivatives, yields a phosphonium salt (LXIX) in which the alpha C-H bond is sufficiently acidic to be removed by a strong base, such as organolithium compound, sodium hydride, sodium amide, lithium or potassium alkoxides. The ylid that results would subsequently reacts with aldehydes or ketones to form the olefin (LXX).⁷⁰

catalyst commonly employed is aluminium chloride with cuprous chloride as carrier, which is not necessary when high pressures are used. Benzene furnishes benzaldehyde in yields up to 90%. Another method, also proposed by Gattermann,⁷² employs a mixture of hydrogen cyanide and hydrogen chloride with or without a catalyst, and permits the introduction of an aldehyde group into phenols and their ethers. A modification of this method employs zinc cyanide as both a convenient source of anhydrous hydrogen cyanide, and also as a catalyst. Phloroglucinol was reacted in this way to produce phloroglucinaldehyde.⁷³ Aluminium chloride may also be added as catalyst when zinc chloride failed to catalyse the reaction, as reported by R. C. Shah⁶⁶ in his preparation of methyl 3-formyl- β -resorcylate (LXVI) from methyl β -resorcylate. Phloroglucinaldehyde may also be obtained by treating phloroglucinol with chlorinated dimethyl sulfide ($\text{CH}_3\text{SCHCl}_2$) in the presence of zinc chloride.⁷⁴

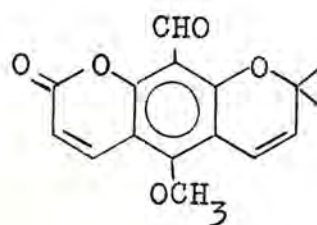
The Vilsmeier-Haack aldehyde synthesis⁷⁵ is also another useful method. N-Methylformanilide reacts with aromatic, heterocyclic and activated ethylenic compounds in the presence of phosphorus oxychloride to produce the intermediate (LXXIV), which upon hydrolysis in acid solution yields the aldehyde (LXXI).



Phloroglucinol monomethyl ether reacted under this condition to produce 2,4-dihydroxy-6-methoxybenzaldehyde (LXXV).⁷⁶ The same reaction applied on benzene also produced benzaldehyde.⁷⁷ The same reaction was employed by C. N. Lam¹⁰ in the formylation of naturally occurring xanthoxyletin (IV) to produce the formylated product (LXXVI).



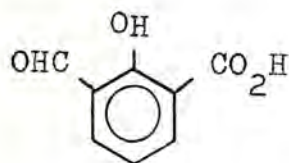
(LXXV)



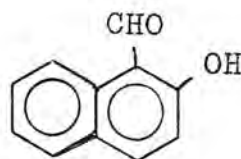
(LXXVI)

There are also some other formylating reactions which require the presence of a phenoxy group to ensure a smooth reaction, such as the Reimer-Tiemann reaction^{78,79} and the Duff-Bills phenolic aldehyde synthesis.^{80,81} The reagent used in the latter reaction is hexamethylenetetramine. When salicylic acid was refluxed with this hexamine, β -aldehydosalicylic acid (LXXVII) was obtained. β -Naphthol in boiling acetic acid

reacted with this reagent to produce the aldehyde (LXXVIII).⁸²

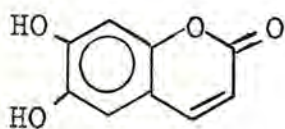


(LXXVII)

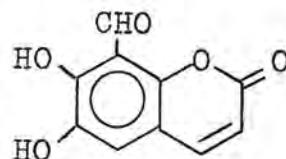


(LXXVIII)

Formylation of hydroxycoumarins has also been reported.⁸³ Using the same reagent, 6,7-dihydroxycoumarin (LXXIX) was formylated to give its 8-formyl derivative (LXXX).

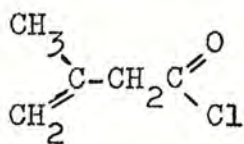


(LXXIX)

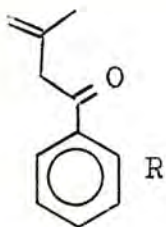


(LXXX)

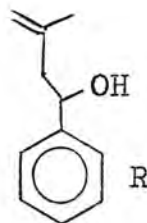
Besides employing the Wittig reaction to introduce the appropriate side chain into the aromatic nucleus, other methods may be used, such as the Friedel-Crafts acylation⁸⁴ with the suitable acyl chloride (LXXXI), the corresponding ketone (LXXXII) formed may then be reduced to the secondary alcohol (LXXXIII), which upon dehydration produces the required double bond (LXXXIII).



(LXXXI)

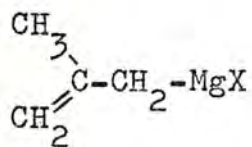


(LXXXII)



(LXXXIII)

Grignard reactions⁸⁵ may also be employed. The Grignard reagent (LXXXIV) with the formyl derivative (LXXI) may give the secondary alcohol (LXXXIII), through which the required product (LXXIII) may be formed.

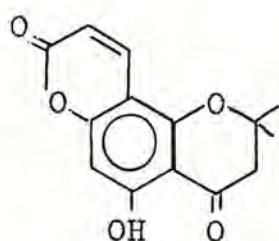


(LXXXIV)

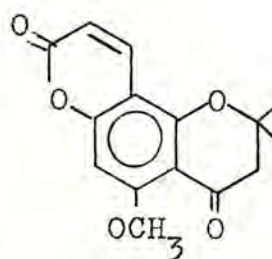
E. Synthesis of the Chromeno- α -Pyrone Systems

Xanthyletin (III) has been synthesized in low yield by the condensation of 3-hydroxy-3-methylbut-1-yne with umbelliferone (XLIII). The simultaneous production of the angular isomer, seselin (VII), showed this type of synthesis to be ambiguous.⁶

Xanthoxyletin (IV) and alloxanthoxyletin (V) have both been synthesized by A. K. Ganguly and co-workers⁸ from 5,7-dihydroxychroman-4-one (XIV). By reacting with ethyl propiolate, both the clausenin (LXIX) and its angular isomer (LXXXV) were produced. Methylation with diazomethane produced the methyl ethers (XIX, LXXXVI). Reduction with sodium borohydride and then dehydration produced the two required products (IV and V).

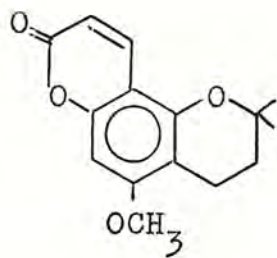


(LXXXV)

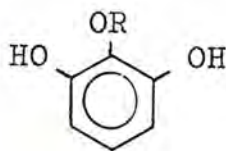


(LXXXVI)

Dihydroalloxanthoxyletin (LXXXVII) was synthesized by A. Robertson and co-workers.^{9,14,24} This synthetic scheme was adopted in the synthesis of the structural skeleton of avicenin (IIb), and will be discussed in a later section.



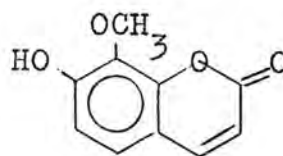
(LXXXVII)



(LXXXVIII)

a. R: -H

b. R: -CH₃



(LXXXIX)

Luvangetin (VI) has been synthesized from pyrogallol (LXXXVIIIa) which was first methylated to the methyl ether (LXXXVIIIb), which was then converted by application of Gattermann reaction to the aldehyde. Cyclization of the aldehyde by Perkin reaction produced 8-methoxyumbelliferone (LXXXIX), which on condensation with 3-hydroxy-3-methylbut-1-yne, was converted to luvangetin (VI) in very low yield.⁶

III. RESULTS and DISCUSSION

In order to build up the three angular ring skeleton of the avicennin structure, two distinct routes could be employed depending on the prior construction of the chromene portion of the structure or the coumarin portion. Followings are the discussions of attempts via both routes.

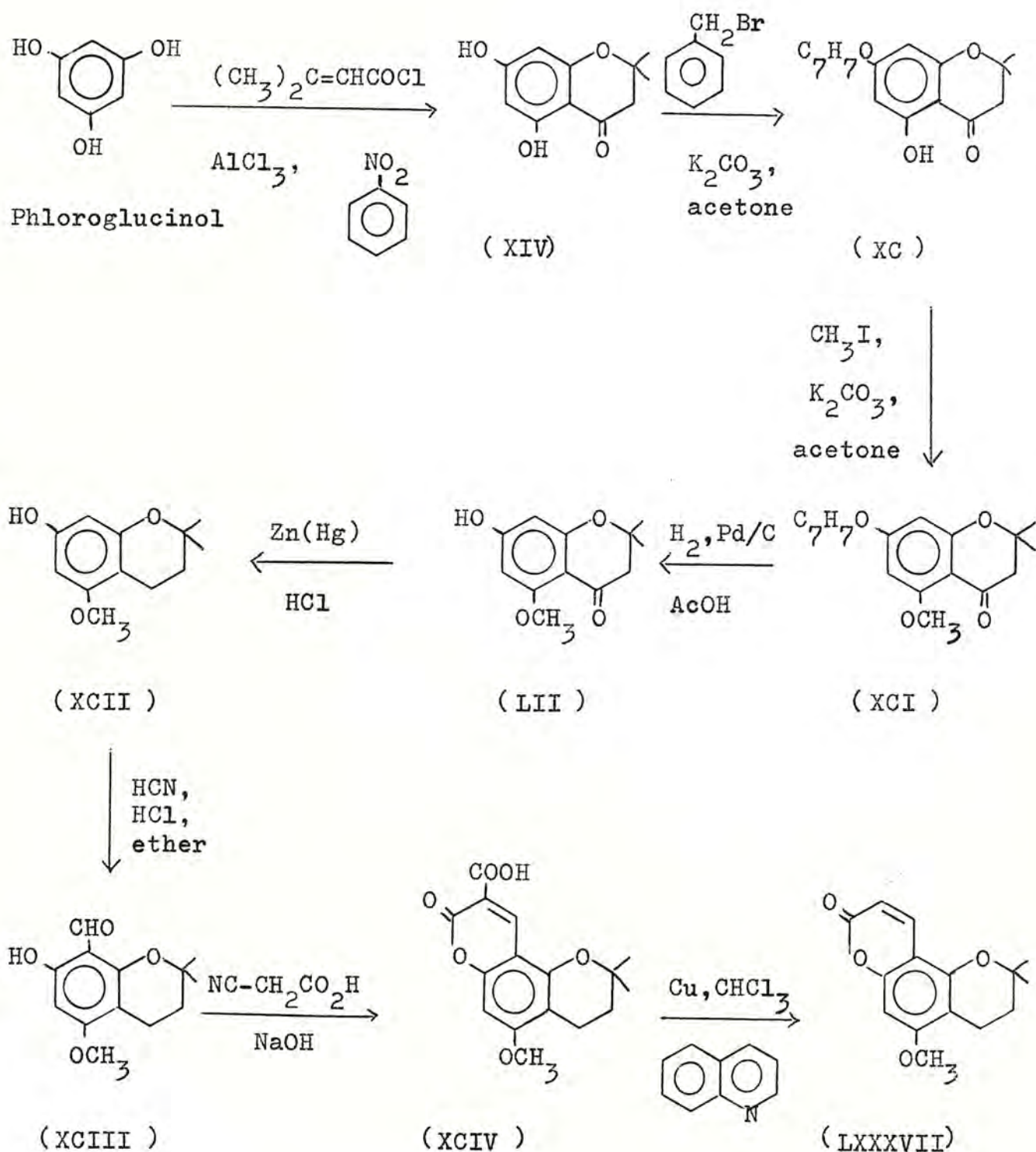
(1) The Chromene Route

As discussed in the previous section, alloxanthoxy-letin (V) has a similar structure as avicennin (IIb) except for the absence of the 3-methyl-trans-butadienyl side chain. Thus the synthesis of alloxanthoxyletin is the first objective, and then through the introduction of the side chain, the complete synthesis of avicennin may be attained.

A. Robertson^{9,14,24} had synthesized dihydroalloxantho-xyletin (LXXXVII) in an unambiguous way, thus his synthetic route was at first adopted for the synthesis of the structural skeleton of avicennin as shown in Scheme 1a.

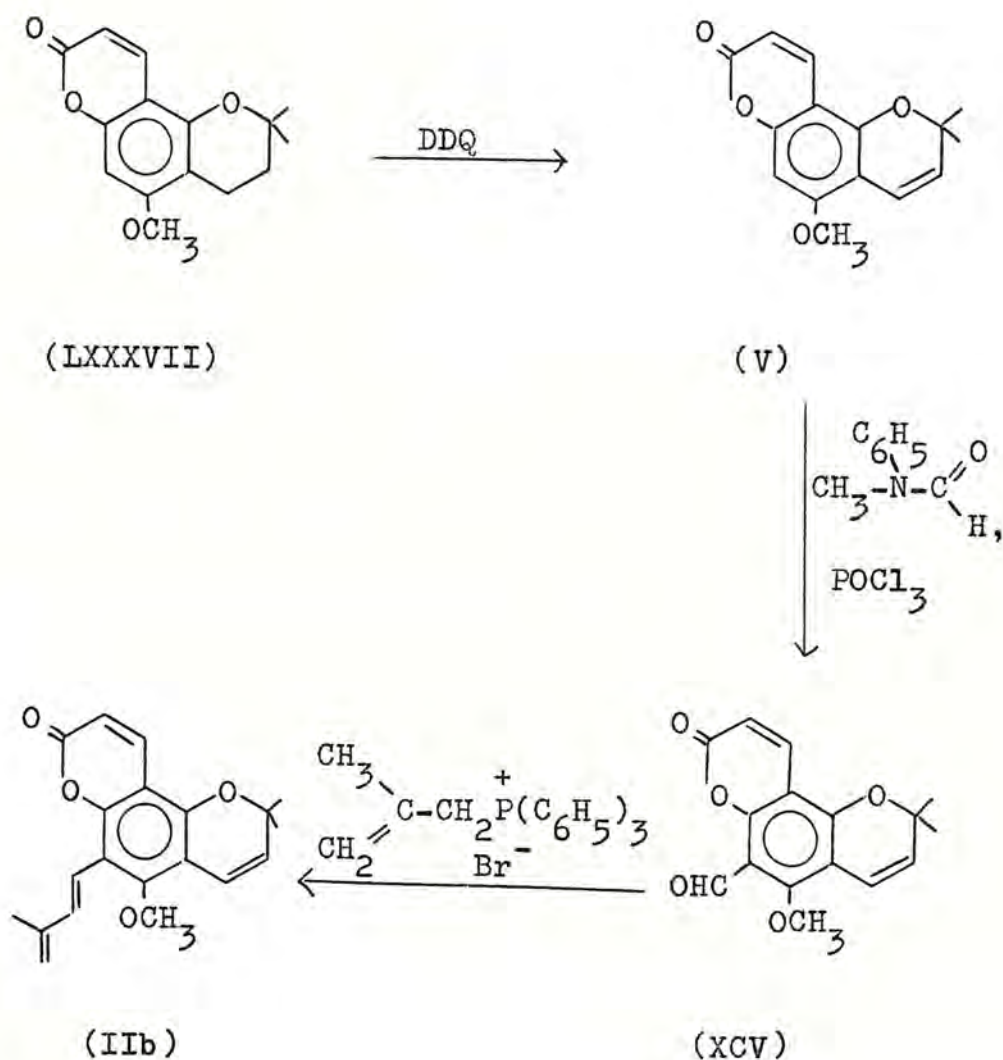
Phloroglucinol was used as the starting material. By the Friedel-Crafts acylation reaction and cyclization with 3,3-dimethylacrylic chloride in the presence of aluminium chloride, 5,7-dihydroxy-2,2-dimethylchroman-4-one (XIV) was obtained. Benzylation with benzyl bromide was employed to protect the more reactive 7-OH group. Then methylation with

methyl iodide produced 7-benzyloxy-5-methoxy-2,2-dimethylchroman-4-one (XCI). Debenzylation was then effected by hydrogenolysis with 10% palladium-charcoal catalyst. The 7-hydroxy-5-methoxy-2,2-dimethylchroman-4-one (LII) thus formed was reduced by Clemmensen reduction to produce the chromane (XCII). Through the Gattermann formylation, only the 8-formyl derivative (XCIII) was obtained. Using cyanoacetic acid as the condensing agent in the Knoevenagel reaction, dihydroalloxanthoxylic-3-carboxylic acid (XCIV) was produced, which was decarboxylated by refluxing with metallic copper in quinoline to form the dihydroalloxanthoxyletin (LXXXVII).



Scheme 1a

The remaining steps to complete the synthesis of avicennin were first proposed as shown in Scheme 1b. Dehydrogenation of dihydroalloxanthoxyletin (LXXXVII) by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) would give alloxanthoxyletin (V). Formylation using Vilsmeier-Haack method, would produce the formyl derivative (XCV), and then through the Wittig reaction with methallyl phosphonium salt, avicennin (IIb) would be obtained.

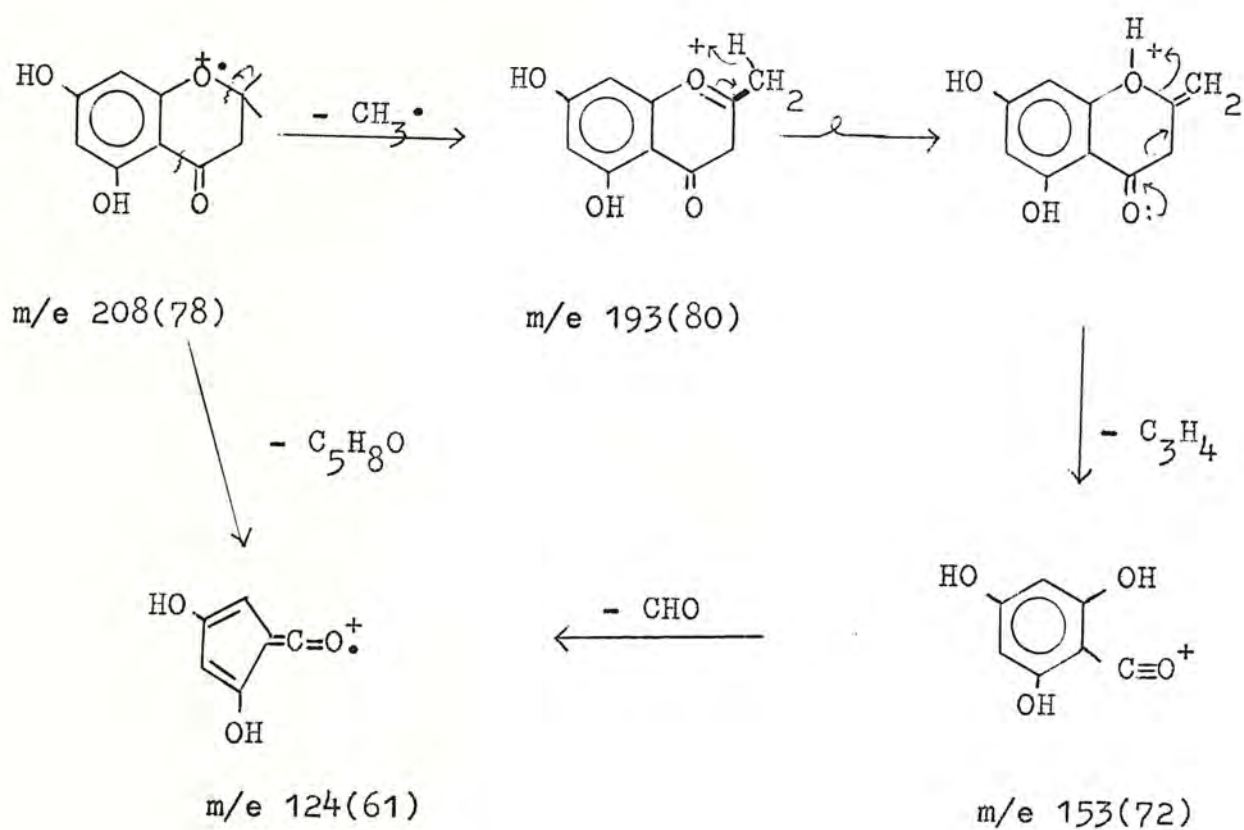


Scheme 1b

Following A. Robertson's method, 3,3-dimethylacrylic chloride was prepared from 3,3-dimethylacrylic acid, which was synthesized with a low yield of 25%. Later the acid was commercially available, and this step was abandoned.

Friedel-Crafts acylation between phloroglucinol and 3,3-dimethylacrylic chloride followed by cyclization gave 5,7-dihydroxy-2,2-dimethylchroman-4-one (XIV). The reaction, originally carried out by A. Robertson¹⁴ used aluminium chloride as the Lewis acid, 3,3-dimethylacrylic chloride as acylating agent, and nitrobenzene as solvent. This reaction was rather time-consuming, since it required a 4-day reaction period, and the extraction of product also required tedious work. Furthermore the yield of this reaction was low, only 15% yield was obtained. Thus another method²⁰ was adopted, which required only 1 day for the reaction, and also the acylating agent was 3,3-dimethylacrylic acid instead of its chloride, thus the acid chloride needed not be prepared. A better yield of 78% was attained. Zinc chloride which was used as the Lewis acid must be freshly fused in the oven. The water of crystallization of phloroglucinol dihydrate was removed by using the drying pistol with refluxing chloroform and potassium hydroxide as the drying agent under reduced pressure (20 mm.). The reaction was very violent when phosphorus oxychloride was added, and must be controlled by cooling in an ice-bath.

In obtaining the product, reaction must be controlled by slow decomposition of phosphorus oxychloride and be kept at ice temperature or else the reaction may become too violent. The product was recrystallized from dilute alcohol to give colorless prisms, m. p. 197-8°. Its infrared spectrum showed a broad band at 3200 cm^{-1} which was due to the phenoxy absorption, and a sharp peak at 1640 cm^{-1} for the carbonyl absorption which was chelated⁸⁶ to the peri-hydroxyl group (LIII). The nmr spectrum (Fig. 1) showed the 6 gem-dimethyl protons at δ 1.40 as a singlet; the 2 methylene protons as a singlet at δ 2.61; the 2 aryl protons as a quartet at δ 5.78-5.81. The two phenoxy protons could not be located definitely, but from the integration, one proton was found around the region δ 1.50-2.50, and the other at δ 3.60-5.00, as broad signals. From its mass spec. the molecular ion appeared at m/e 208, corresponding to the molecular formula of 5,7-dihydroxy-2,2-dimethylchroman-4-one (XIV), $\text{C}_{11}\text{H}_{12}\text{O}$, molecular weight 208. Major fragmentations⁸⁷ were shown in Scheme 2. Intensities were given in parenthesis.



Scheme 2

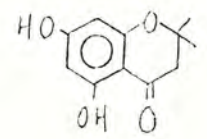
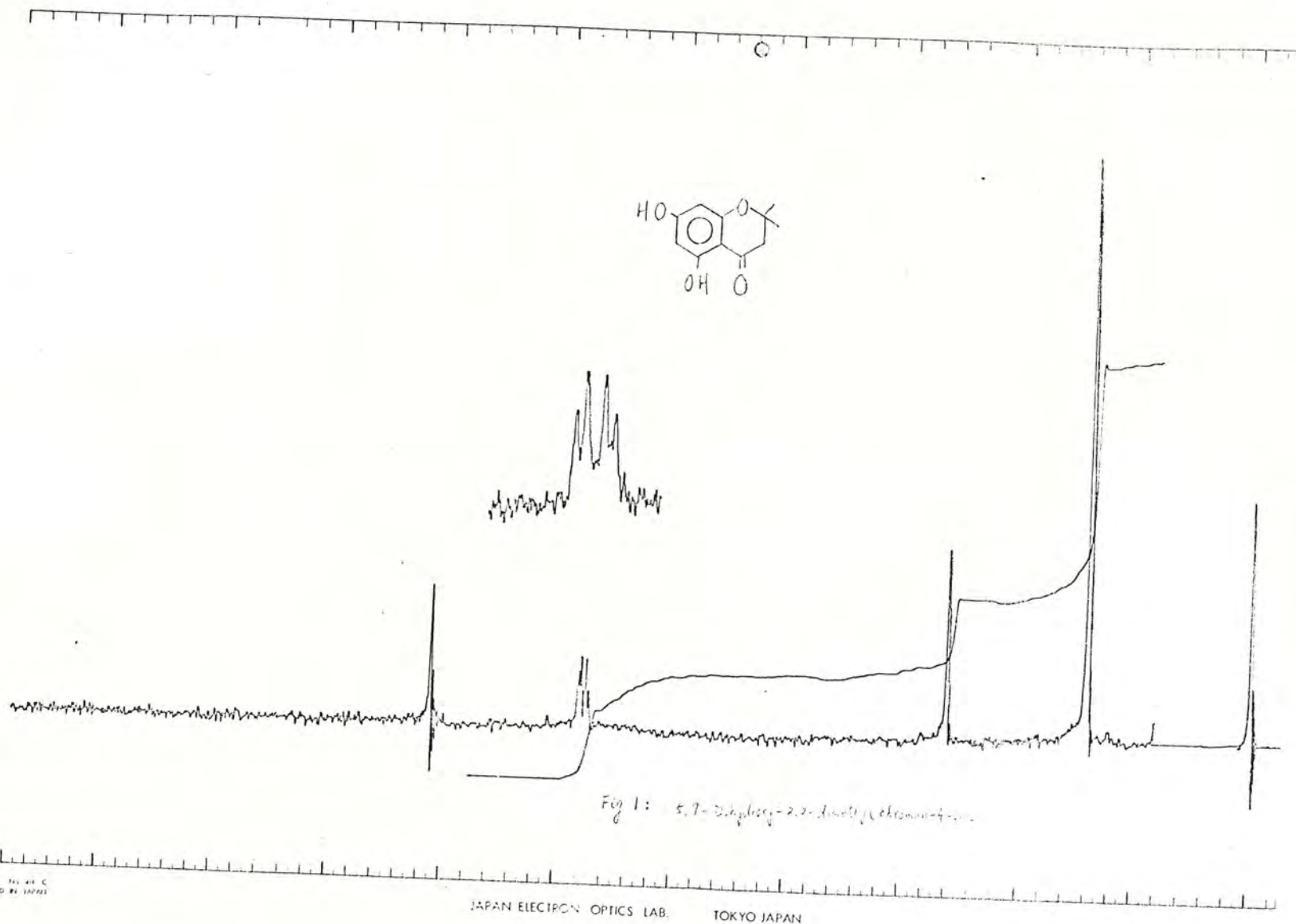


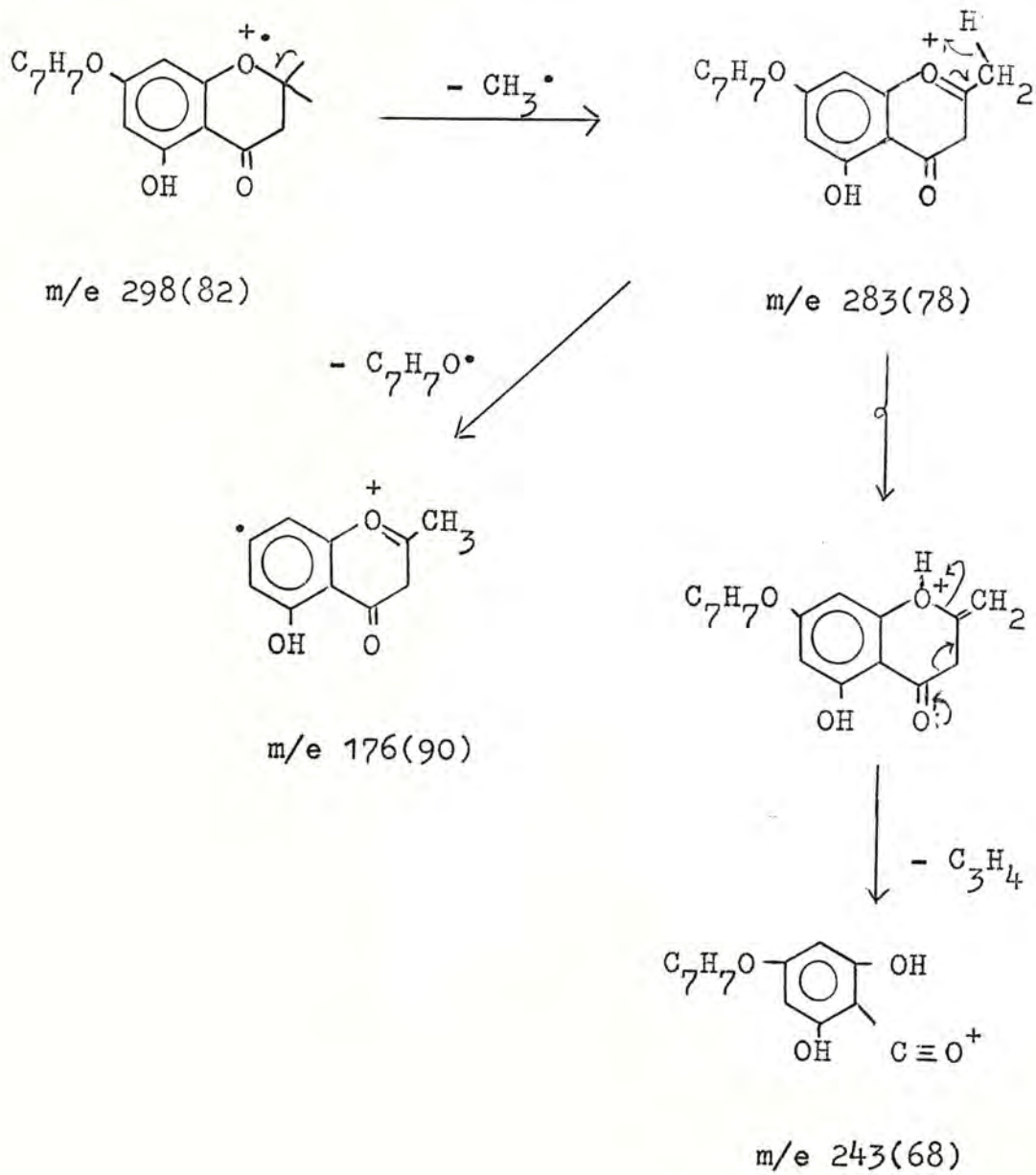
Fig 1: 5,7-Dihydroxy-2,2-dimethylchroman-4-one

Fig. 1: 5,7-Dihydroxy-2,2-dimethylchroman-4-one

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Selective benzylation of the 7-position served as a blocking reaction. This is to prevent the more reactive 7-position being methylated in the next step, thus producing the unwanted isomer. The reaction²⁴ proceeded with great ease in very high yield (95%). The 7-benzyloxy derivative (XC) was obtained as colorless needles, m. p. 133°. Its infrared spectrum showed only a very small band at 3500 cm⁻¹ which was the chelated phenol group absorption. Again the carbonyl absorption appeared at 1640 cm⁻¹. The nmr spectrum (Fig. 2) showed the same characteristic peaks as the 5,7-dihydroxy compound (XIV), except that only one broad signal was observed at δ 6.00-7.00. In addition there was a singlet signal for the 5 aromatic protons of the benzyl group at δ 7.18, as well as another singlet for the 2 benzyl protons at δ 4.92. The mass spec. showed the molecular ion at m/e 298, which agreed with the molecular formula of 7-benzyloxy-5-hydroxy-2,2-dimethylchroman-4-one (XC), C₁₈H₁₈O₄, molecular weight 298. The fragmentations were shown in Scheme 3.



Scheme 3

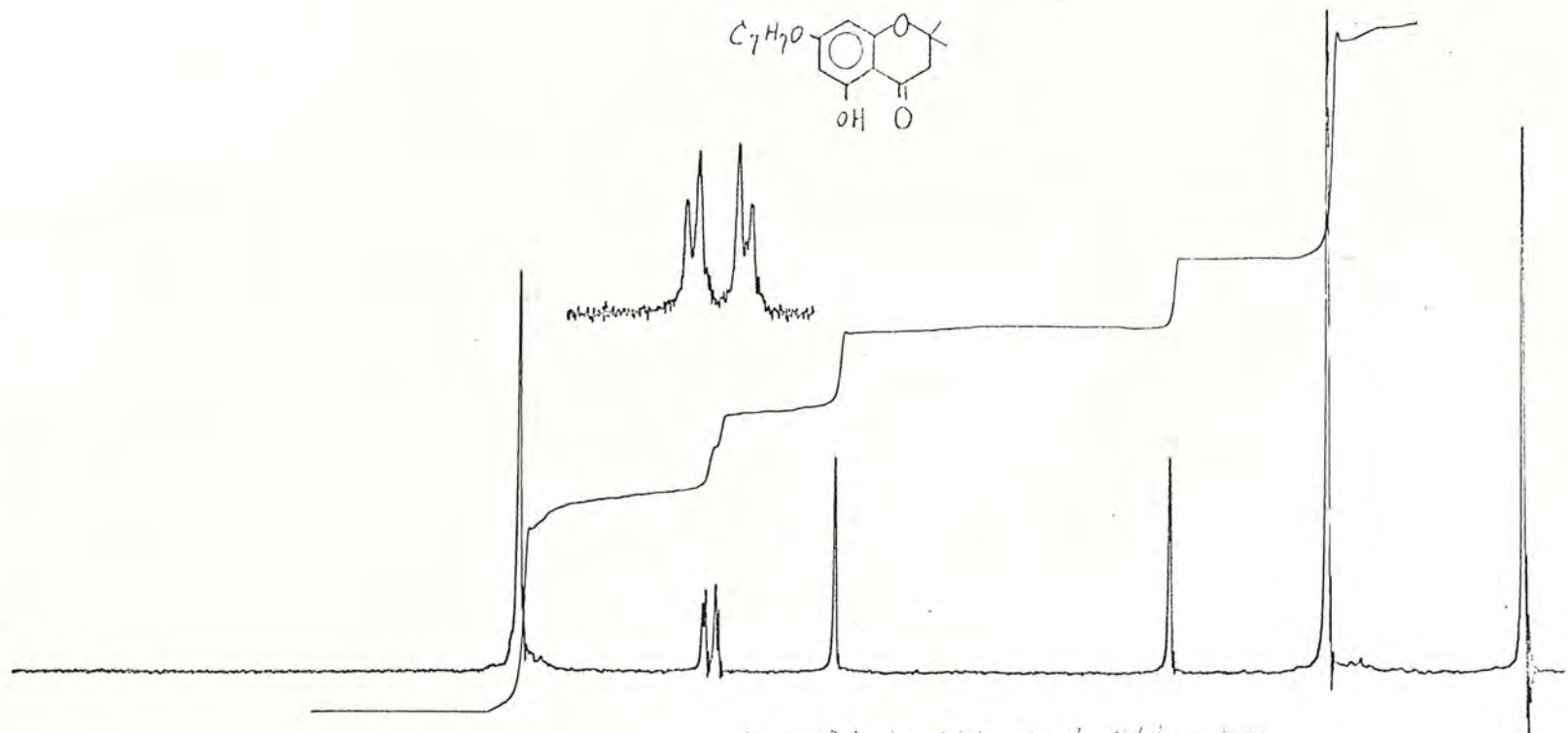
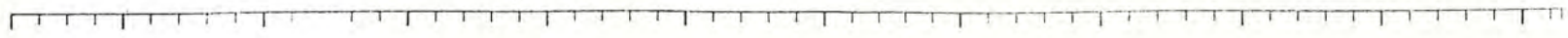


Fig. 2: 7-Benzoyloxy-5-hydroxy-2,2-dimethylchroman-4-one

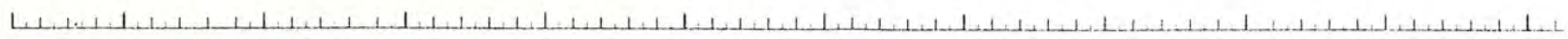
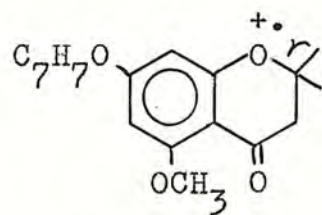


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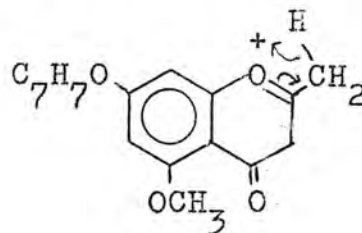
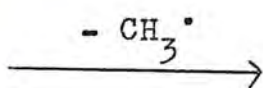
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Fig. 2: 7-Benzoyloxy-5-hydroxy-2,2-dimethylchroman-4-one

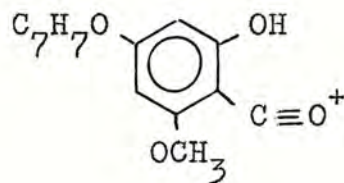
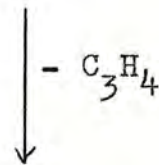
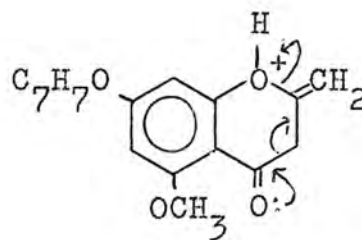
The synthesis of 7-benzyloxy-5-methoxy-2,2-dimethylchroman-4-one (XCI) was a little more difficult than previous steps, since the 5-OH group was chelated. Great excess of methyl iodide was required to ensure a reasonable yield,²⁴ and often the product was very hard to be purified. The experiment was repeated using diazomethane⁸⁸ which gave only a poor yield. Dimethyl sulfate was found to be a better methylating reagent and the product recrystallized from absolute alcohol to give colorless prisms, m. p. 110-111°, in about 90% yield. Its infrared spectrum showed the carbonyl absorption at 1690 cm^{-1} as compared with 1640 cm^{-1} for the parent compound, which indicated that the carbonyl group was free from chelation. The nmr spectrum (Fig. 3) showed an additional singlet for the 3 methoxy protons at δ 3.68, in addition to the peaks observed in compound (XC). From the mass spec., the molecular ion appeared at m/e 312, which agreed with its molecular formula $\text{C}_{19}\text{H}_{20}\text{O}_4$, molecular weight 312. The fragmentations were shown in Scheme 4.



m/e 312(72)



m/e 297(51)



m/e 256(53)

Scheme 4

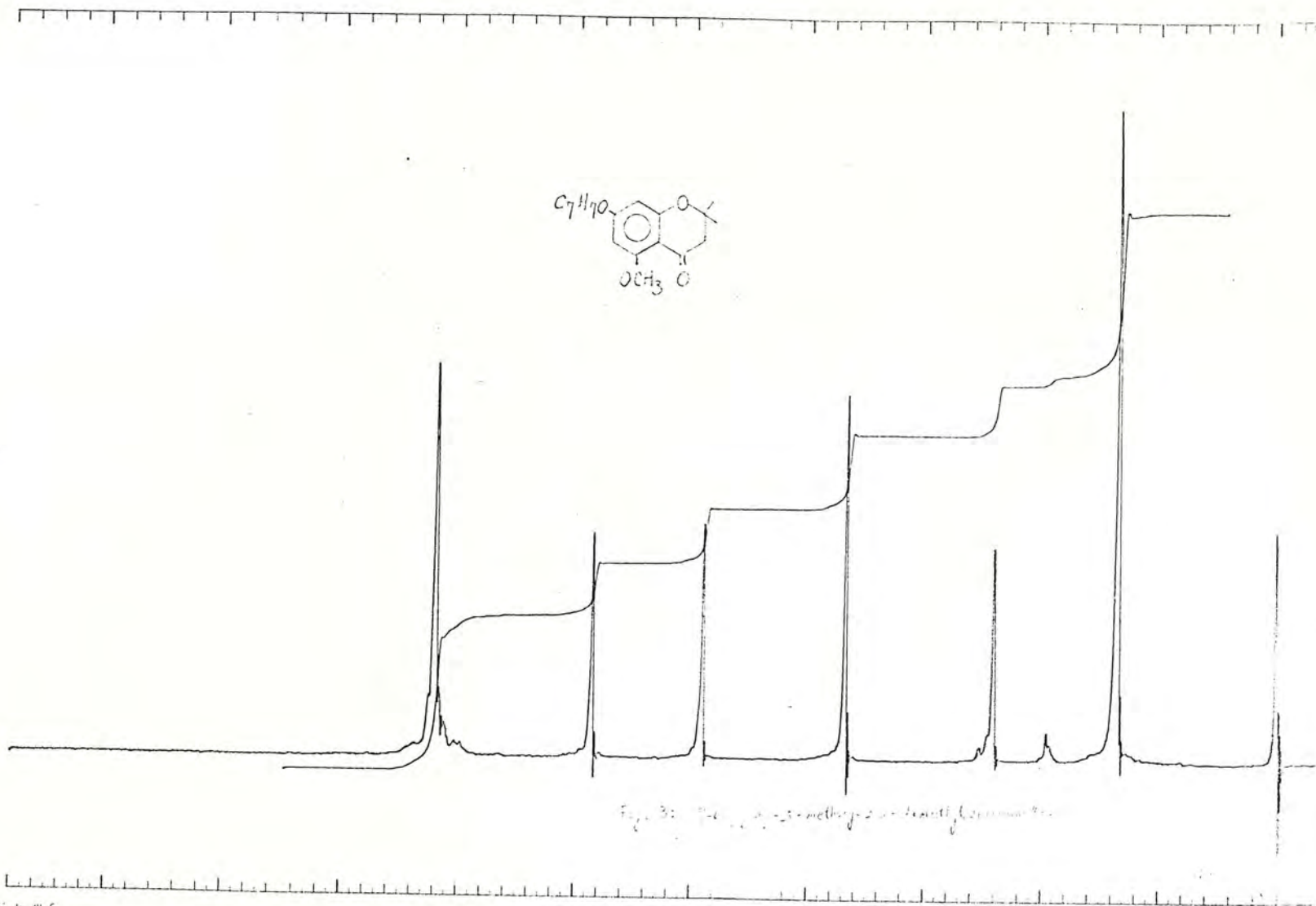


Fig. 3: 7-benzyloxy-5-methoxy-2,2-dimethylchroman-4-one

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Fig. 3: 7-Benzyloxy-5-methoxy-2,2-dimethylchroman-4-one

Then came the step for the removal of the blocking group which encountered much difficulties. Debenzylation was repeated many many times, but the result was often not reproducible. In many cases the starting material was recovered. The catalyst: 10% palladium on charcoal was freshly prepared and stored in a vacuum desiccator.⁸⁹ The solvent: glacial acetic acid was redistilled. The starting material was thoroughly dried. Still the reaction did not proceed satisfactorily. The reaction was repeated under various temperatures and pressures, and it was found (from the successful experiments) that the optimum conditions were at around 40° and hydrogen pressure at about 21 lb./sq. in. (1.2 atm.). The catalyst was found to be pyrolytic, and often for each gramme of palladium chloride used for the preparation of the catalyst (about 6 g. obtained), only one or two successful experiments were able to be carried out. Concentrated hydrochloric acid, and perchloric acid were added to the reaction mixture with the hope that better hydrogenolysis would occur, but without any apparent success. When platinum oxide (Adam's catalyst) was employed in the hydrogenolysis, only phloroglucinol was obtained. Debenzylation without using catalyst had also been attempted: under various conditions and refluxing for various length of time in solvent systems such as conc. HCl in benzene, in absolute alcohol, in glacial acetic acid, and in mixtures of these reagents, no consistent results could be

obtained. In some cases, the starting material was recovered; in other cases not only the benzyl group was removed, but also the chroman-4-one ring, the methoxy group, were cleaved, thus producing phloroglucinol again. Recently by using absolute alcohol as solvent instead of glacial acetic acid, debenzyla-
tion seemed to proceed better with palladium-charcoal catalyst.

7-Hydroxy-5-methoxy-2,2-dimethylchroman-4-one (LII) recrystallized from absolute alcohol as colorless rectangular prisms, m. p. $206-8^{\circ}$. Its infrared spectrum showed the bands due to -OH absorption at 3250 cm^{-1} which indicated that the band found in the 5,7-dihydroxy derivative (XIV) was mainly due to the 7-OH group, and that of the carbonyl absorption appeared at 1680 cm^{-1} . The 5 aromatic protons and the two benzyl protons were absent from its nmr spectrum (Fig. 4).

The next step was the Clemmensen reduction. No crystallizable product was obtained, only dark oil was formed. In view of the shortage of the starting material and the difficulties in the debenzylation step, no further attempt had been repeated.

Another method of reduction was employed. It was hoped that by using lithium aluminium hydride as the reducing agent, 7-hydroxy-5-methoxy-2,2-dimethylchroman-4-one (LII) may be reduced to form the corresponding chroman-4-ol (XCVI). Then through dehydration, the chromene (XCVII) may be obtained.

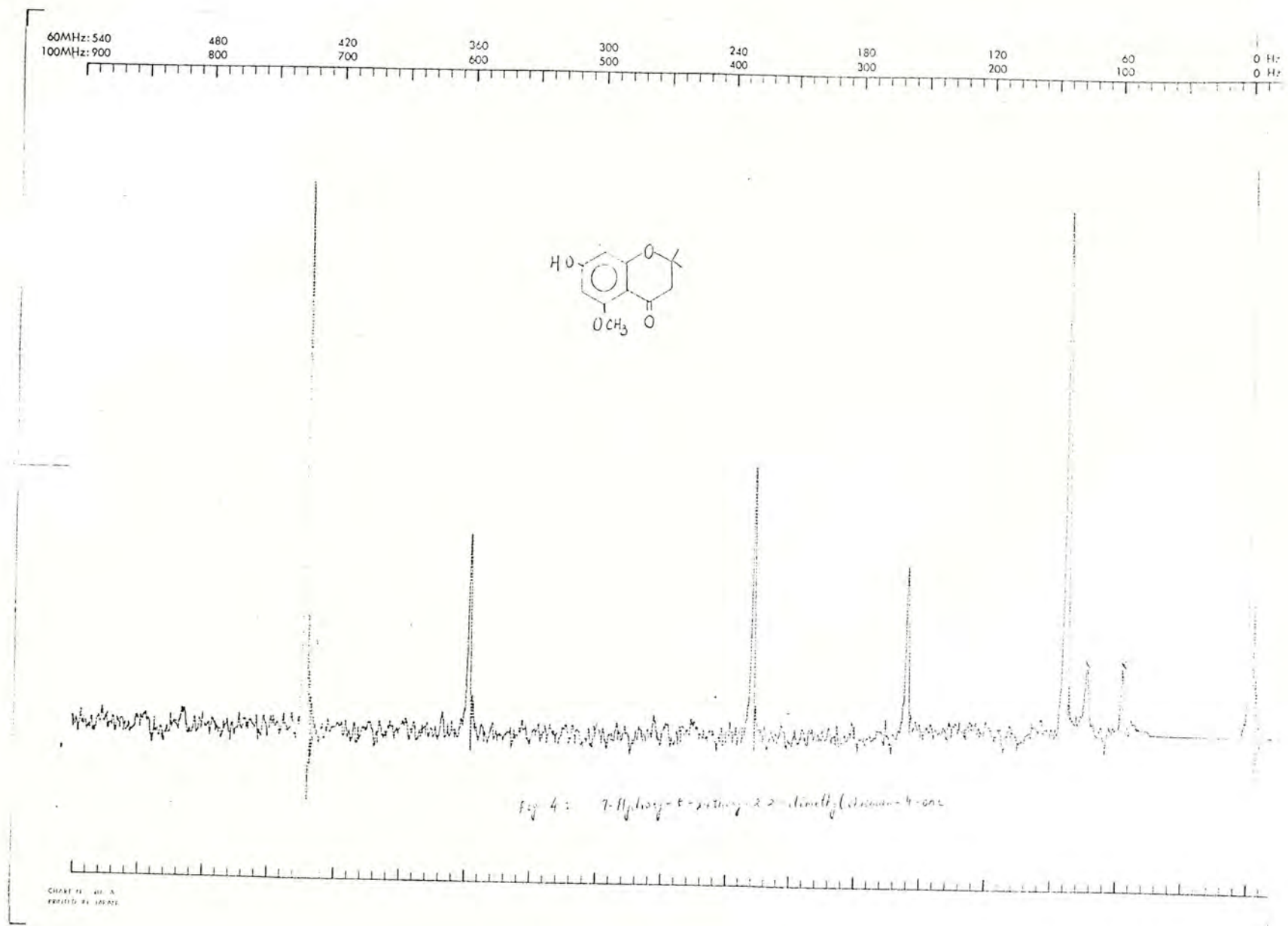
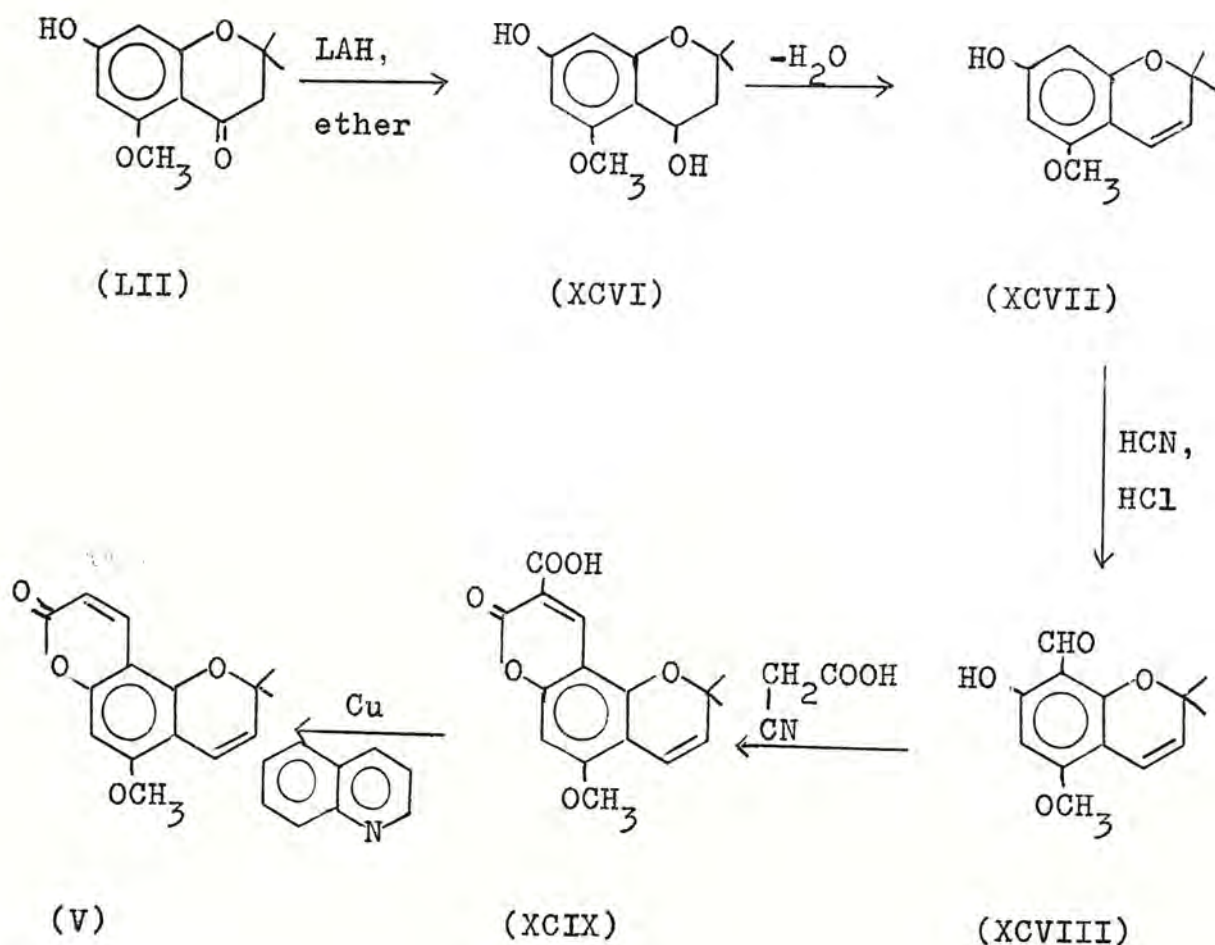


Fig. 4: 7-Hydroxy-5-methoxy-2,2-dimethylchroman-4-one

Also in this way, the originally proposed step for the dehydrogenation of dihydroalloxanthoxyletin (LXXXVII) with DDQ may be omitted. The proposed route is summarised in Scheme 5.



Scheme 5

The reduction was carried out without much success. The presence of the free phenoxy group which formed complexes with lithium aluminium hydride,²⁶ caused the reactant to precipitate out from the ether layer, and as a result, no further reduction could occur, thus the starting material was recovered. When tetrahydrofuran was used as solvent instead, the starting material was dissolved and reaction seemed to occur. No starting material was recovered, but the product obtained was very difficult to purify, and the yellow pigment could not be removed. The product recrystallized from chloroform as yellow crystals, m. p. 265°. Its infrared spectrum showed a broad absorption band for the hydroxyl and the phenoxy group. The carbonyl absorption was no longer found. Because of the presence of the impurities, the nmr spectrum (Fig. 5) did not show well-defined signals. But still it could be observed that the 6 gem-dimethyl protons appeared as a singlet at δ 1.40; the 2 methylene protons as a doublet at δ 3.50; the 3 methoxy protons as a singlet at δ 3.85; the α -proton of the hydroxyl group as a multiplet at δ 4.60; the hydroxyl group as a broad signal at δ 5.38; and the 2 aryl protons as a singlet at δ 6.10.

Dehydration with *p*-toluenesulfonic acid in refluxing benzene produced no crystallizable product, thus this route was abandoned.

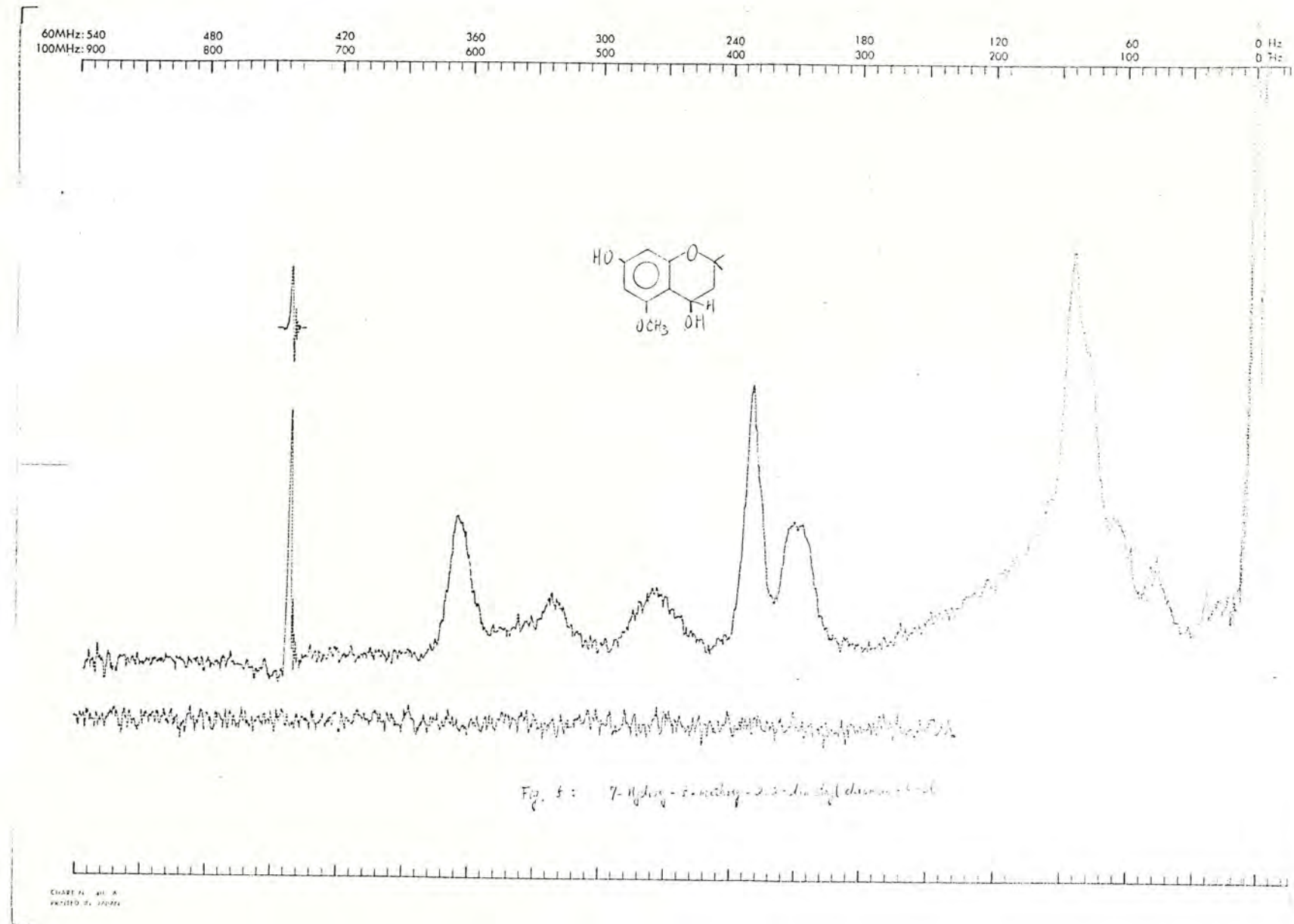
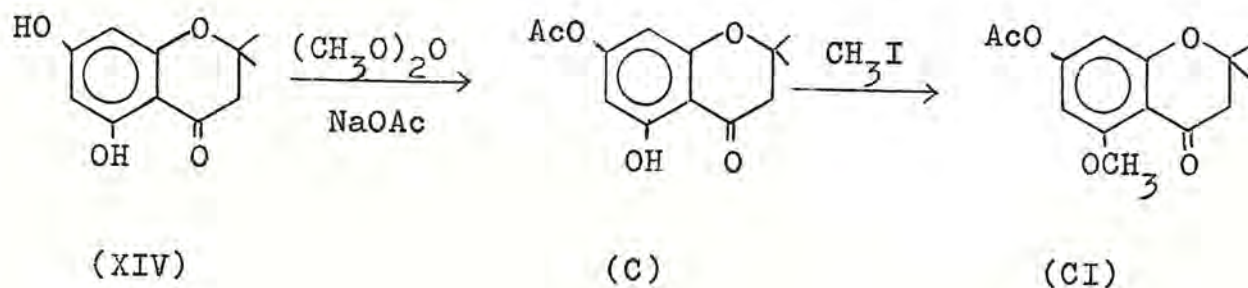


Fig. 5: 7-Hydroxy-5-methoxy-2,2-dimethylchroman-4-ol

In view of the difficulties encountered in the debenzoylation, it was thought worthwhile to employ other protecting groups instead of the benzyl group. The acetyl derivative was thought to be a good protecting group because it can serve two functions. While the more reactive 7-position is protected from methylation in the following step, the presence of the acetoxy group would avoid the complex formation with lithium aluminium hydride in the reduction. Furthermore, the acetyl group may also be removed at the same time when the carbonyl group of the chroman-4-one is reduced to the chroman-4-ol, thus forming the desired 7-hydroxy-5-methoxy-2,2-dimethylchroman-4-ol (XCVI).



Acetylation of the 5,7-dihydroxy-2,2-dimethylchroman-4-one (XIV) produced the 7-acetoxy derivative (C) as colorless crystals, m. p. 164° . Its infrared spectrum showed the band due to the ester carbonyl absorption at 1760 cm^{-1} , and that of the carbonyl absorption of the chroman-4-one appeared at 1630 cm^{-1} . The nmr spectrum (Fig. 6) showed an additional singlet for the 3 methyl protons of the acetyl group at $\delta\ 2.35$ in addition to those obtained for the 5,7-dihydroxy-2,2-dimethyl-

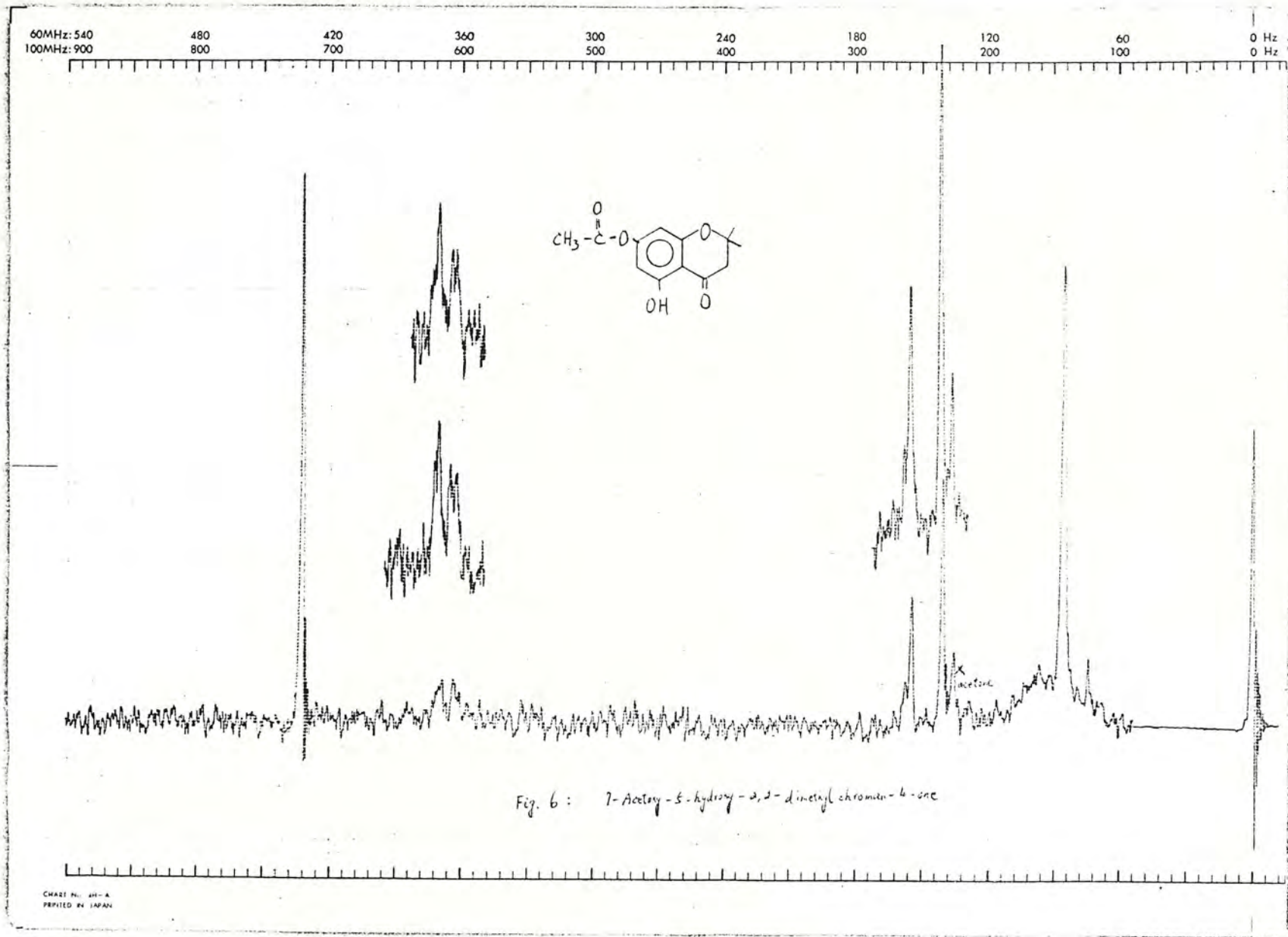


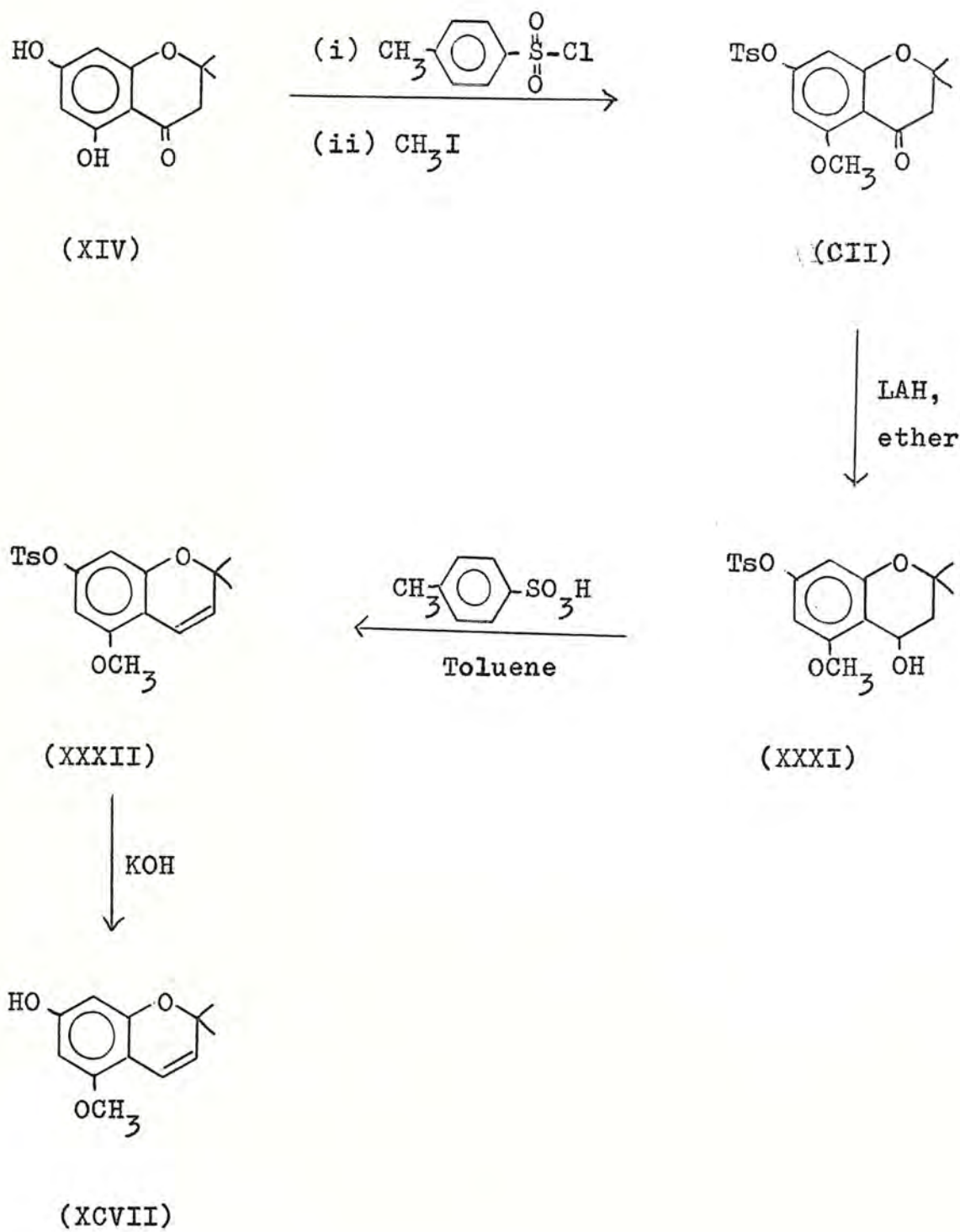
Fig. 6: 7-Acetoxy-5-hydroxy-2,2-dimethylchroman-4-one

chroman-4-one (cf. Fig. 1).

It was hoped that by methylation of the 5-OH group, the 7-acetoxy-5-methoxy-2,2-dimethylchroman-4-one (CI) may be obtained, and then through reduction with lithium aluminium hydride, the acetyl group would be removed, and also the corresponding chroman-4-ol (XCVI) would be formed. Then through dehydration, 7-hydroxy-5-methoxy-2,2-dimethylchroman-4-one (XCVII) may then be obtained.

However, methylation of this compound produced no crystallizable product, thus no further reaction could be carried out.

Basing on the same hypothesis, another new protecting group, the *p*-toluenesulfonyl derivative was used.²⁷ 5,7-Dihydroxy-2,2-dimethylchroman-4-one (XIV) was first reacted with *p*-toluenesulfonyl chloride in acetone in the presence of K_2CO_3 , and then methylated with methyl iodide to yield the 5-methoxy-7-(*p*-tolylsulfonyloxy)-2,2-dimethylchroman-4-one (CII). Reduction with lithium aluminium hydride in ether would produce the corresponding chroman-4-ol (XXXI). Dehydration employing *p*-toluenesulfonic acid in refluxing toluene, would produce 5-methoxy-7-(*p*-tolylsulfonyloxy)-2,2-dimethylchromene (XXXII). Under alkaline hydrolysis, the blocking group would be removed to produce the desired chromene (XCVII). Scheme 6 summarises the reaction steps.



Scheme 6

During the preparation of 5-methoxy-7-(p-tolylsulfonyloxy)-2,2-dimethylchroman-4-one (CII), compound (XIV) was refluxed with p-toluenesulfonyl chloride for 5 hours; only an oil was formed. When this oil was allowed to react with excess methyl iodide, the desired product (CII) was obtained. This compound (CII) recrystallized from aqueous methanol in form of colorless prisms, m. p. 152° in 30% overall yield. Its infrared spectrum showed a very sharp carbonyl and sulfonyl absorption at 1680 cm^{-1} . Apart from the signals obtained for the 7-hydroxy-5-methoxy-2,2-dimethylchroman-4-one (LII), its nmr spectrum (Fig. 7) showed the p-methyl protons of the tosylate group at δ 2.42 as a singlet, and the 4 aromatic protons of the tosylate group at δ 7.28-7.72 as a quartet.

Reduction of the chroman-4-one (CII) with lithium aluminium hydride in ether produced the corresponding chroman-4-ol (XXXI). The product recrystallized from aqueous methanol to form yellow crystals, m. p. 148° , in 70% yield. The chroman-4-one (CII) was not very soluble in ether, so after reduction, when the complex was decomposed by dilute sulfuric acid, some crystals remained undissolved. This was the unreacted starting material. But still the reaction proceeded more smoothly than that of the reduction of 7-hydroxy-5-methoxy-2,2-dimethylchroman-4-one (LII). The product would recrystallize out only when very dilute methanol solution was used, otherwise yellow oil was obtained. The infrared spectrum

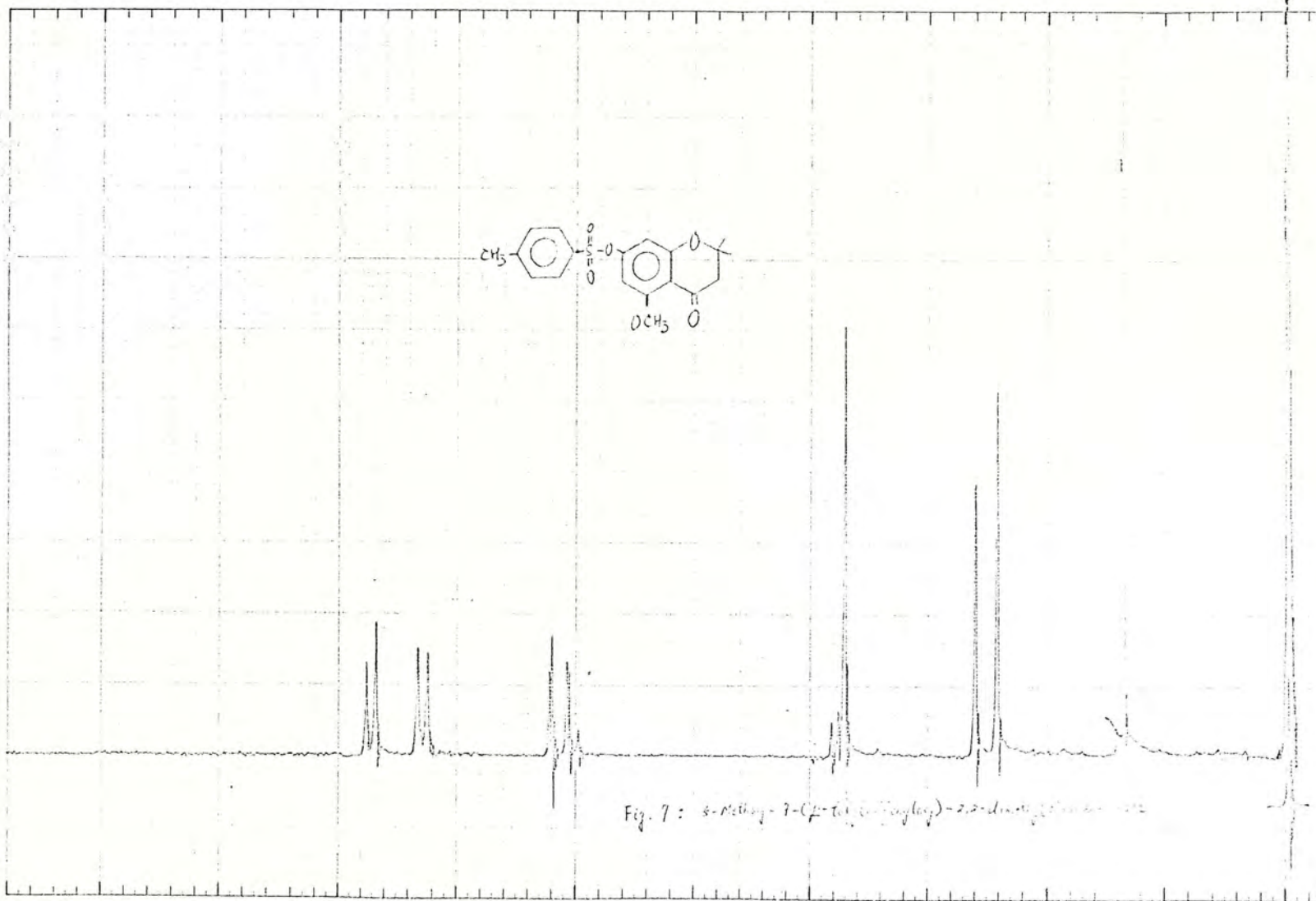


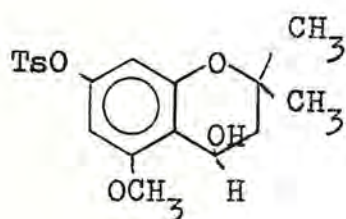
Fig. 7: 5-Methoxy-7-(p-tolylsulfonyloxy)-2,2-dimethylchroman-4-one

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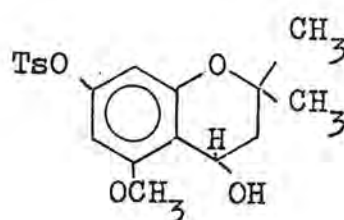
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Fig. 7: 5-Methoxy-7-(p-tolylsulfonyloxy)-2,2-dimethylchroman-4-one

showed a sharp absorption of the hydroxyl group at 3560 cm^{-1} , and a much weakened sulfonyl absorption at 1680 cm^{-1} . Its nmr spectrum (Fig. 8) showed a doublet signal for the 6 gem-dimethyl protons. This may be due to the fact that both isomers (CIII a,b) may be formed during reduction, and due to the difference of influence exerted by a cis-OH group and a trans-OH group, the methyl signal would be split.



(CIII a)



(CIII b)

The singlet signal for the 2 methylene protons was also changed into a doublet at $\delta 1.95-2.05$, due to the presence of an α -proton. The signal for the α -proton of the alcohol appeared at $\delta 4.90-5.10$ as a triplet, and the hydroxyl proton appeared as a singlet at $\delta 3.25$.

Dehydration of the chroman-4-ol (XXXI) was carried out with *p*-toluenesulfonic acid in refluxing toluene. The product, 5-methoxy-7-(*p*-tolylsulfonyloxy)-2,2-dimethylchromene (XXXII) was recrystallized from methanol in form of yellow plates, m. p. 98° , in 60% yield. Its infrared spectrum no longer showed the hydroxyl absorption, and again the weakened sulfonyl absorption was observed at 1680 cm^{-1} . Its nmr spectrum (Fig. 9) showed a singlet signal for the 6 gem-dimethyl protons at

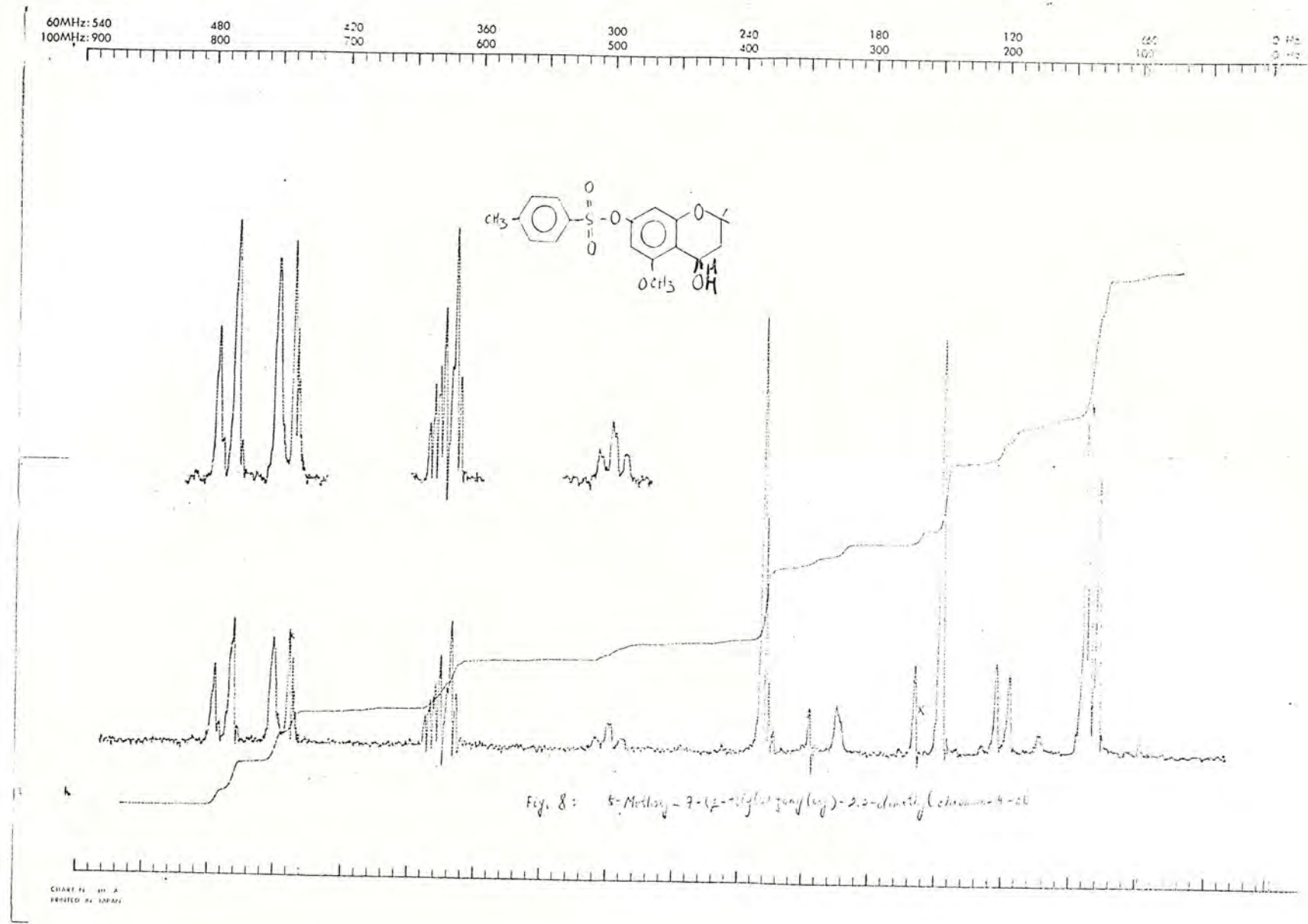


Fig. 8: 5-Methoxy-7-(p-tolylsulfonyloxy)-2,2-dimethylchroman-4-ol

δ 1.35; a singlet for the p-methyl protons of the tosylate group at δ 2.45; a singlet for the 3 methoxy protons at δ 3.72; a pair of doublets replacing the methylene protons at δ 5.50-5.68 and δ 6.58-6.75 for the vinyl protons (2); and the two groups of aryl protons at δ 6.10-6.35 and δ 7.40-7.95.

Detosylation was carried out by alkaline hydrolysis with potassium hydroxide. Detosylation occurred readily, but unfortunately the separation of the p-toluenesulfonic acid from the required chromene (XCVII) could only be achieved by means of column chromatography (silica gel). The acid obtained was in form of rectangular prisms, m. p. 104° , with a sharp absorption at 1670 cm^{-1} in its infrared spectrum, thus confirming the fact that the absorption observed in the fore compounds was not only due to the carbonyl absorption. The chromene (XCVII) was recrystallized from aqueous alcohol, in form of yellow plates, m. p. 188° . Its infrared spectrum showed no carbonyl absorption nor sulfonyl absorption at 1680 cm^{-1} , only the aromatic absorption at 1600 cm^{-1} was observed, and also there was the phenoxy group absorption found at 3500 cm^{-1} .

From literature⁶¹ it was found that by employing v. Pechmann reaction, cyclization of the coumarin ring would occur with phenoxy compounds when using malic acid in the presence of sulfuric acid. The chromene obtained (XCVII) was allowed to react with malic acid in the presence of 73% sul-

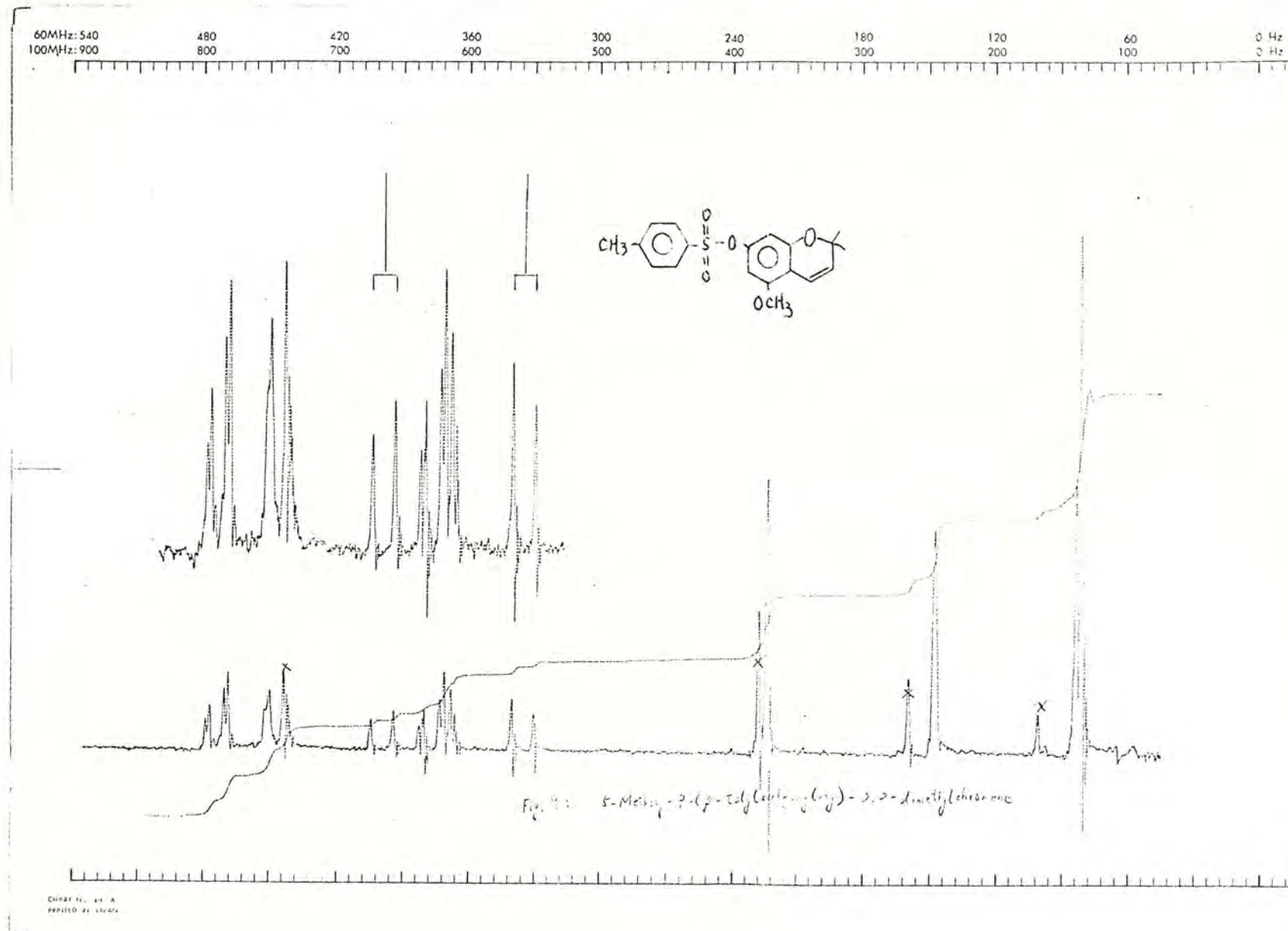
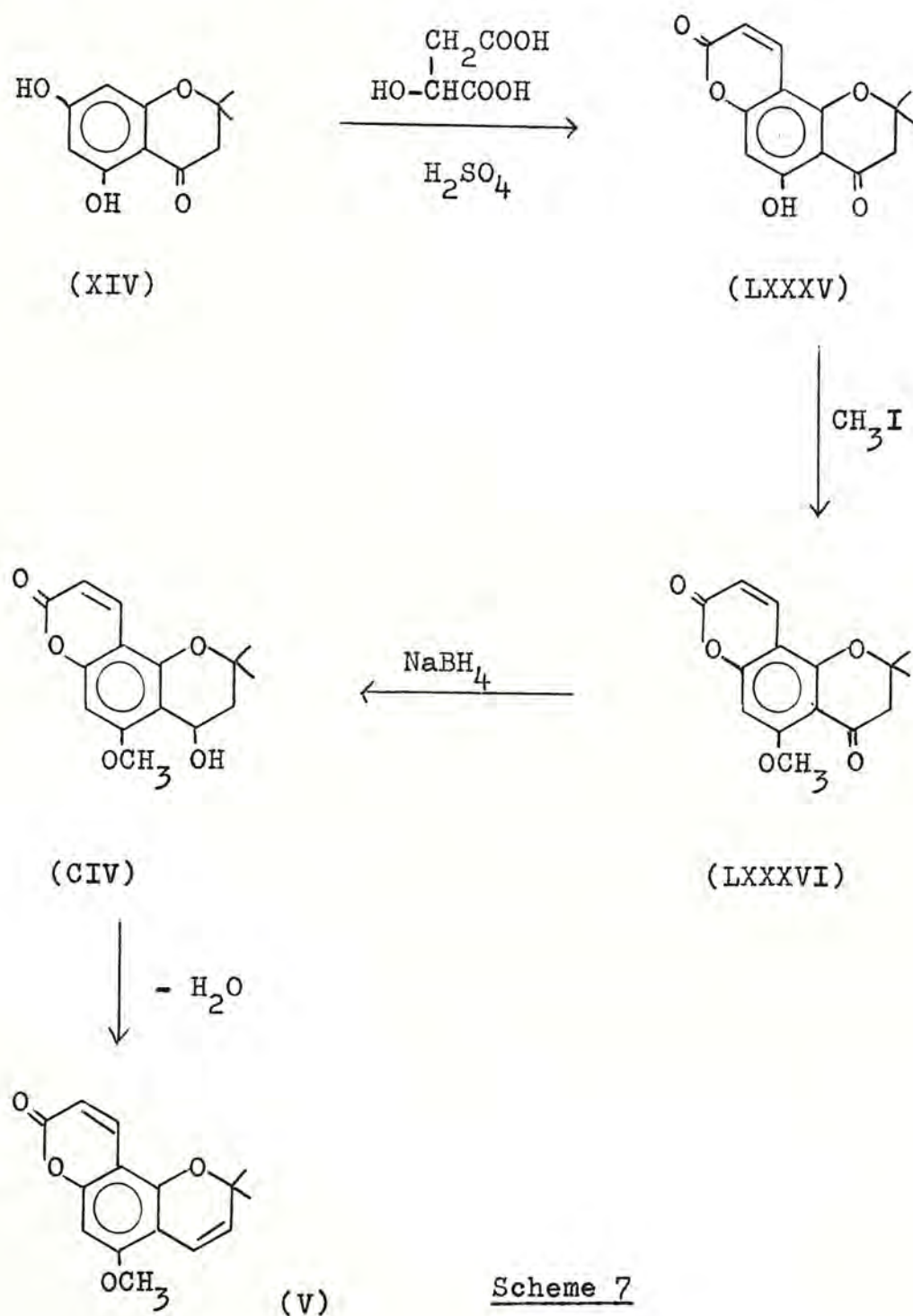


Fig. 9: 5-Methoxy-7-(p-tolylsulfonyloxy)-2,2-dimethylchromene

furic acid, but without success. When using concentrated sulfuric acid instead of 73% sulfuric acid, dark oil was produced. When reacting 7-hydroxy-5-methoxychromene (XCVII) in 73% sulfuric acid with malic acid at 40°, dark brown precipitate was obtained, which could not be purified to produce crystallizable product. This reaction was still being carried out, with the hope that alloxanthoxyletin (V) may be obtained.

In order to avoid the addition and removal of a protecting group at the more reactive 7-position of the 5,7-dihydroxy-2,2-dimethylchroman-4-one (XIV), still another route may be followed (Scheme 7). Cyclization with malic acid may produce the coumarin (LXXXV) which upon methylation, reduction and dehydration, again alloxanthoxyletin (V) may be obtained.



Scheme 7

A. K. Ganguly and co-workers⁸ had succeeded by using compound (XIV) and ethyl propiolate in the presence of zinc chloride to cyclise the coumarin ring but producing two isomers (LXIX, LXXXV). The same reaction was hoped to occur when reacting compound (XIV) with malic acid in the presence of sulfuric acid. Since the isomers could be separated by chromatography on silica gel, the required angular isomer (LXXXV) may be obtained.

5,7-Dihydroxy-2,2-dimethylchroman-4-one (XIV) was reacted with malic acid in the presence of 73% sulfuric acid. Although two isomers were expected to be formed, but only one product was obtained, having m. p. 220°, which was the required structure, i. e. the angular isomer. This reaction could only be explained by the fact that the reaction was allowed to react at a lower temperature than that reported by A. K. Ganguly (100°), who also used ethyl propiolate instead of malic acid. Furthermore the 8-position of the chroman-4-one (XIV) may be more reactive than the 6-position; this would be expected by the fact that only the 8-formyl derivative (XCIII) of 7-hydroxy-5-methoxy-2,2-dimethylchromane (XCII) was produced as the sole product when carrying out the Gattermann formylation.⁹ But in the latter case, the steric hindrance due to the 5-methoxy group may play an important part also, so the exact reason for the formation of only one isomer could not be predicted. When the experiment was allowed to react at

at a higher temperature: 80° , a mixture of the 2 isomers was obtained. Thus the 6-position must be less reactive, since it required a more drastic reacting condition to react.

The angular isomer (LXXXV) recrystallized from aqueous alcohol in form of yellow crystals, m. p. 220° . Its infrared spectrum showed the bands due to the coumarin absorption at 1720 cm^{-1} , and the carbonyl absorption of the chroman-4-one ring at 1640 cm^{-1} , which indicated that the 5-OH group was still chelated to the carbonyl group. The nmr spectrum (Fig. 10) showed a singlet for the 6 gem-dimethyl protons at $\delta\ 1.66$; a singlet for the 2 methylene protons at $\delta\ 3.00$; a pair of doublets for the vinyl protons of the coumarin ring at $\delta\ 6.40-6.60$ and $\delta\ 8.25-8.40$ ($J = 10$ cps), and a singlet for the 1 aryl proton at $\delta\ 6.72$.

The methylation of the angular isomer (LXXXV) was carried out using methyl iodide in excess. The reaction mixture was refluxed for 8 hours, and the product was recrystallized from acetone in form of colorless crystals, m. p. $193-4^{\circ}$. Its infrared spectrum showed the bands due to the coumarin absorption at 1720 cm^{-1} , and the carbonyl absorption at 1680 cm^{-1} , which indicated that the 5-OH group was free from chelation. The nmr spectrum (Fig. 11) showed a singlet for the 6 gem-dimethyl protons at $\delta\ 1.47$; a singlet for the 2 methylene protons at $\delta\ 2.70$; a singlet for the 3 methoxy protons at $\delta\ 3.88$; a pair of doublets for the vinyl protons of the

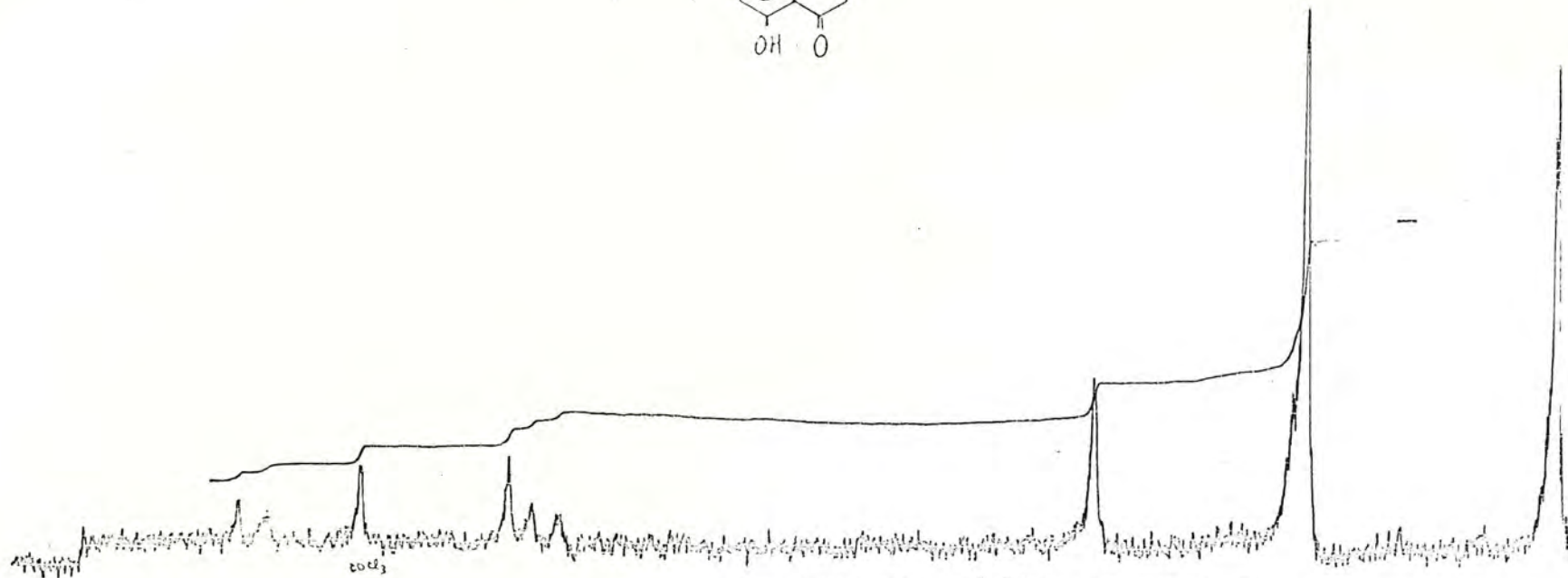
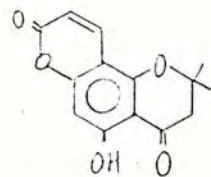


Fig. 10: 6,7-Dihydro-6,6-dimethyl-9-hydroxy-8-oxo-pyrano[2,3-f] coumarin

Fig. 10: 6,7-Dihydro-6,6-dimethyl-9-hydroxy-8-oxo-pyrano[2,3-f] coumarin

coumarin ring at δ 5.59-6.14 and δ 7.74-7.90 (\underline{J} = 10 cps), and a singlet for the 1 aryl proton at δ 6.27.

Reduction of the methoxy derivative of the angular isomer (LXXXVI) was attempted, but only the starting material was recovered. This reaction will still be attempted, and should this reaction be successful, through dehydration, alloxanthoxyletin (V) may then be obtained.

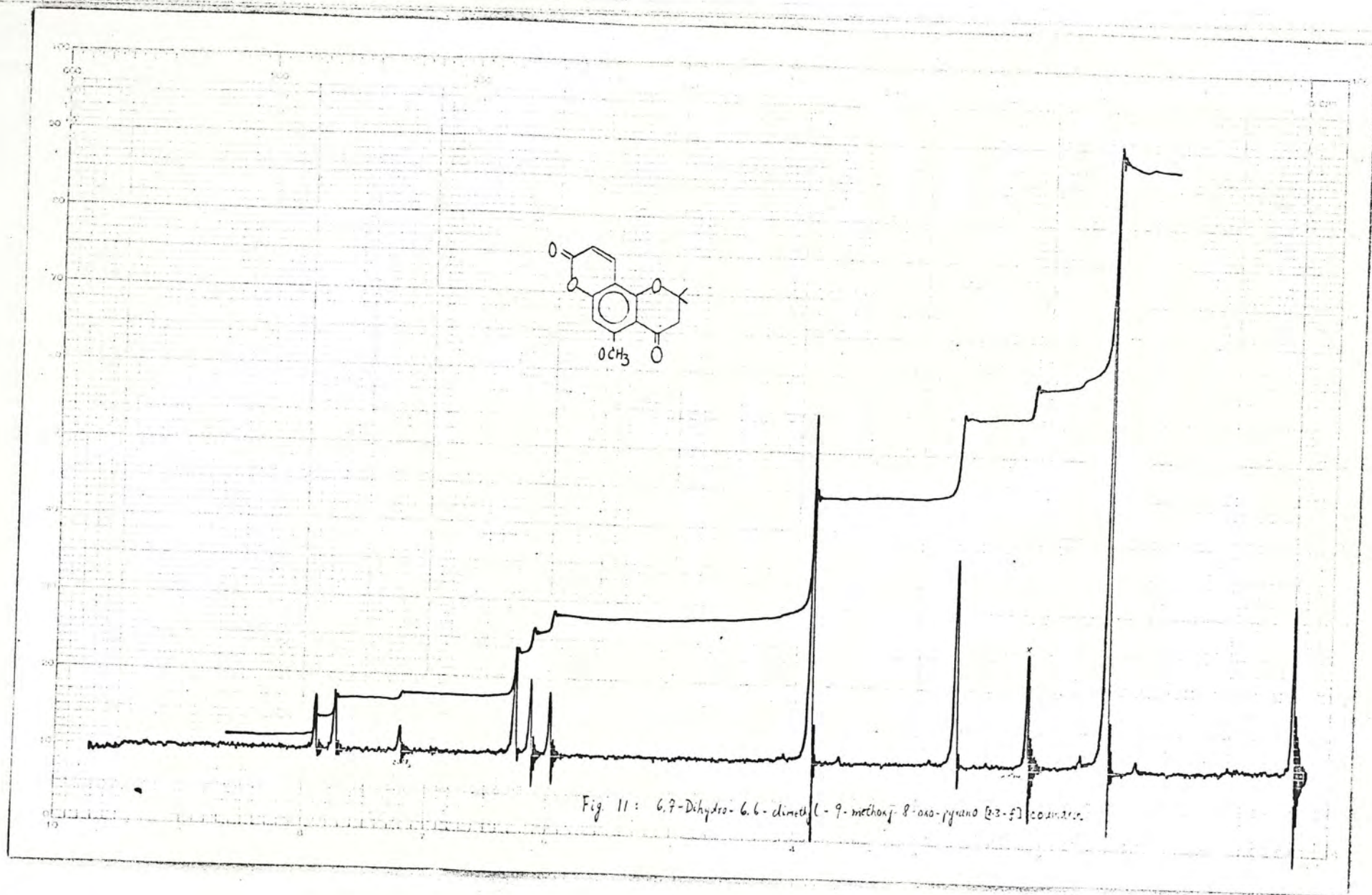
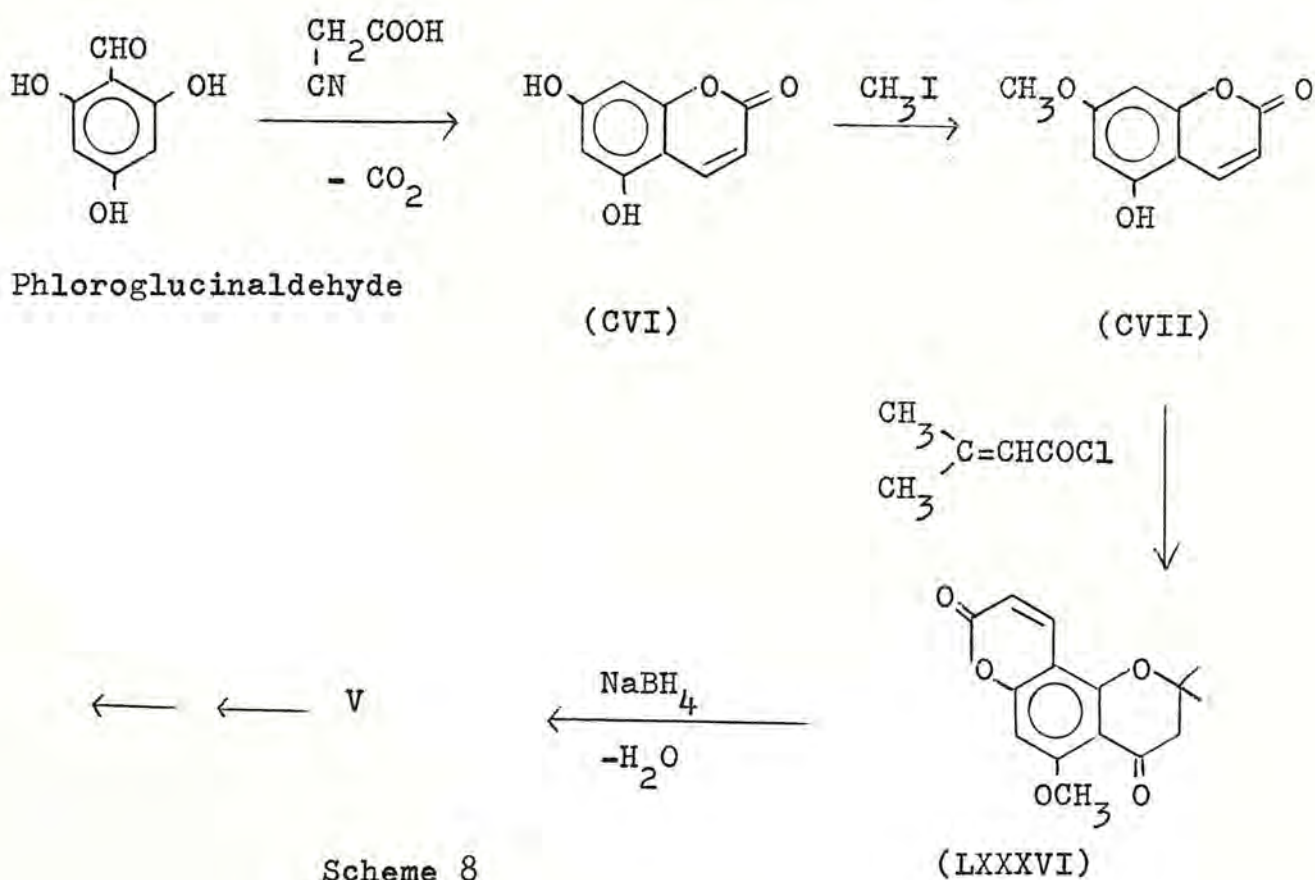


Fig. 11: 6,7-Dihydro-6,6-dimethyl-9-methoxy-8-oxo-pyrano[2,3-f]coumarin

(2) The Coumarin Route

Due to the difficulties encountered in the debenzyla-
tion of 7-benzyloxy-5-methoxy-2,2-dimethylchroman-4-one (XCI),
other routes were investigated. One obvious route was to
synthesize the 5,7-dihydroxycoumarin (CVI) and follow the
route according to Scheme 8. Methylation of the more reactive
7-OH group would produce the 5-hydroxy-7-methoxycoumarin (CVI)
since it was reported^{48a} that the 7-position was more reactive,
then cyclization of the chroman-4-one ring would produce the
correct angular skeleton (LXXXVI). Reduction of the carbonyl
group followed by dehydration would produce alloxanthoxyletin
(V). Then the remaining steps for the introduction of the
side chain may be carried out.



Scheme 8

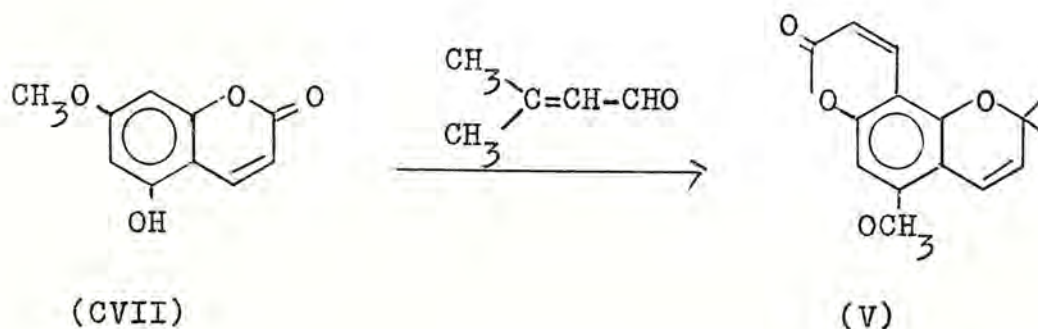
The reaction between phloroglucinaldehyde and cyanoacetic acid was not successful. Only brown oil was obtained. This may be due to the fact that phloroglucinaldehyde was too reactive, and may polymerize.

As discussed before, coumarin may be obtained through the reaction of phenolic compound and malic acid in the presence of sulfuric acid (the v. Pechmann reaction). Phloroglucinol was used as the starting material. The reaction was carried out under various conditions. At first 73% sulfuric acid was used and the reaction mixture was stirred at room temperature for several hours. The starting material was recovered. Concentrated sulfuric acid was then used instead, but the product obtained was very difficult to be recrystallized, and also it has a very high melting point: 345° . It was believed that the product was the sulfonated derivative of 5,7-dihydroxycoumarin. Later 73% sulfuric acid was again employed (to prevent sulfonation to take place) at a higher reaction temperature: 40° . When the reaction mixture was stirred for 6 hours, yellow precipitate was obtained. The precipitate recrystallized from aqueous alcohol in form of yellow needles, m. p. 290° . Its infrared spectrum showed the bands due to the coumarin absorption at 1760 cm^{-1} and 1720 cm^{-1} , and the phenoxy absorption appeared at 3440 cm^{-1} .

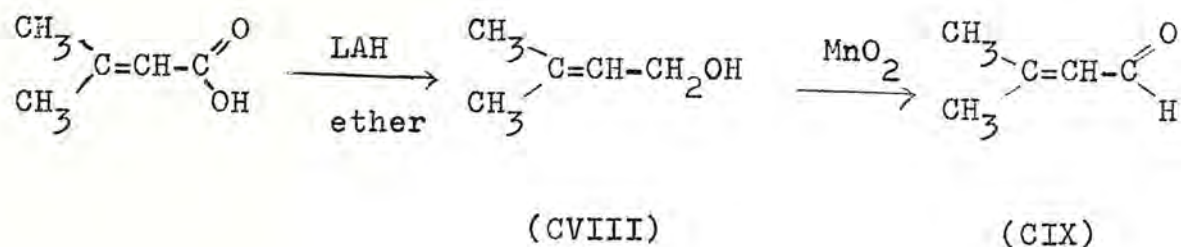
Methylation of 5,7-dihydroxycoumarin (CVI) was carried out using methyl iodide. The 7-methoxy derivative (CVII) re-

crystallized from aqueous alcohol as yellow crystals, which decomposed at around 220° . Its infrared spectrum showed the bands due to the phenoxy absorption at 3500 cm^{-1} , and that of the coumarin at 1760 cm^{-1} and 1730 cm^{-1} .

From literature⁴⁷ it was found that dimethylchromenylation would occur by reacting the phenoxy group with 3-methylbut-2-enal. Thus one reaction would be able to introduce the chromene ring into the basic structure, instead of having to cyclise the chroman-4-one ring followed by reduction and dehydration in order to produce the required chromene. Should this reaction be successful, alloxanthoxyletin would be produced directly.



Before this reaction could be carried out, 3-methylbut-2-enal has to be prepared.^{47c} 3,3-Dimethylacrylic acid was used as the starting material. It was first reduced by lithium aluminium hydride in ether to form the colorless liquid, 3,3-dimethylallyl alcohol (CVIII), b. p. $138^{\circ}/760\text{ mm.}$, in 43% yield.



Then 3-methylbut-2-enal (CIX) was prepared by oxidation of the alcohol (CVIII) with active manganese dioxide. This product was a yellow liquid, with boiling range of 120-130°.

Dimethylchromenylation of 5-hydroxy-7-methoxycoumarin (CVII) was carried out, but only the starting material was recovered. This reaction will still be attempted with the hope that alloxanthoxyletin may be obtained.

(3) Conclusion

The synthesis of avicennin has not been completed, although various routes may lead to the formation of alloxanthoxyletin (V). Due to the late arrival of the reagents for the introduction of the side chain into the aromatic nucleus, the test reactions for the Vilsmeier-Haack formylation, and the Wittig reaction has not yet been attempted.

Up to the present moment, pure 7-hydroxy-5-methoxy-2,2-dimethylchromene (XCVII) has been obtained. By reacting with malic acid, alloxanthoxyletin (V) may be formed. Reduction of the methoxy derivative of the angular isomer (LXXXVI) would still be tried, and then through dehydration, again alloxanthoxyletin (V) may be obtained. From the coumarin route, the dimethylchromenylation will again be carried out. It is hoped that this reaction may be successful, which again may produce alloxanthoxyletin (V).

Various routes were still under investigation, but the complete synthesis of the expected product, avicennin, has yet to be investigated.

IV. EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope and are reported uncorrected. Infrared spectra were taken with a Perkin-Elmer Model 337 Grating Infrared Spectrophotometer. Ultraviolet spectra were taken with a Perkin-Elmer Model 137 UV Spectrophotometer. Nmr spectra were measured by JEOL, with JMN-MH-100 Nmr Spectrometer. Molecular weights were confirmed by JEOL, with JMS-01SG Mass Spectrometer.

3,3-Dimethylacrylic Acid⁹⁰

Mesityl oxide (40 g., 0.4 mole) and potassium hypochlorite⁹¹ (200 g., 1.84 moles) in water (1.2 litres), were reacted in dioxane (80 ml.) at room temperature for 12 hours. Sodium bisulfite (about 2 g.) was added to react with the excess hypochlorite solution (tested by KI-starch paper). The solution was acidified with 50% H₂SO₄ (80 ml.) to Congo Red paper and was extracted with ether (8 x 250 ml.). Evaporation of the solvent gave a residue (brown liquid) which was distilled under reduced pressure (30 mm.) and the portion with b. p. 100-115° was collected. After cooling, yellow crystals were obtained. Recrystallization from petroleum ether (60-80°) gave colorless needles (10 g.) of 3,3-dimethylacrylic acid (25% yield), m. p. 69.5-70° (Lit.,⁹⁰ 70°).

This acid could also be prepared but in a very poor yield from a mixture of malonic acid (40 g., 0.4 mole), acetone (120 ml.) and acetic anhydride (40 ml.), which was refluxed over a steam-bath for 3 days. Distillation of the acetone and acetic acid gave a brown oil from which only very little of the crystalline acid was obtained.⁹²

3,3-Dimethylacrylic Chloride⁹³

Thionyl chloride (11 ml., 0.15 mole) was added slowly to anhydrous 3,3-dimethylacrylic acid (10 g., 0.1 mole). After gas evolution, the mixture was kept at 95° in an oil-bath for 15 min. The excess SOCl_2 was removed by water pump, and the residue was fractionally distilled. The portion with b. p. 59-61°/30 mm. gave a colorless liquid (9.5 g.) of 3,3-dimethylacrylic chloride (78% yield).

5,7-Dihydroxy-2,2-Dimethylchroman-4-one (XIV)¹⁴

(i) Anhydrous phloroglucinol (16.2 g., 0.13 mole) was added with agitation at 0° to a solution of aluminium chloride (15.2 g., 0.11 mole) in nitrobenzene (200 ml.). 3,3-Dimethylacrylic chloride (11.5 g., 0.1 mole) was added slowly. The reaction mixture was then stirred for 4 days at room temperature. After addition of ice (150 g.) and dil. HCl (100 ml.), the product together with nitrobenzene was extracted with ether. Nitrobenzene was removed by steam distillation. The

precipitate deposited from the aqueous solution was recrystallized from CHCl_3 . Colorless prisms (8 g.) of 5,7-dihydroxy-2,2-dimethylchroman-4-one (15% yield), m. p. $198-9^\circ$ (Lit.,¹⁴ $198-9^\circ$) was obtained.

(ii) Anhydrous phloroglucinol (10 g., 0.08 mole), freshly fused ZnCl_2 (40 g.), and 3,3-dimethylacrylic acid (8 g., 0.8 mole) were dissolved in POCl_3 (120 ml.). The reaction mixture was kept at room temperature ($25-30^\circ$) for 24 hours. It was then poured onto crushed ice. The solid separated out was filtered, dried and recrystallized from aq. alcohol. Colorless prisms (13.5 g.) of 5,7-dihydroxy-2,2-dimethylchroman-4-one (78% yield), m. p. $197-8^\circ$, was obtained.²⁰

The ir spectrum (KBr disc) showed the bands due to -OH at 3200 cm^{-1} (broad), and the carbonyl absorption at 1640 cm^{-1} (sharp).

The uv spectrum (CHCl_3) showed the max. at 243 and 297 $\text{m}\mu$; ϵ , 5,410 and 20,800.

Nmr (100 MHz, CDCl_3): δ 1.40 (s, 6, gem-dimethyl), 1.5-2.5 (m, 1, phenoxy), 2.61 (s, 2, methylene), 3.60-5.60 (m, 1, phenoxy), and 5.78-5.81 (q, 2, aryl). [Fig. 1]

Mass Spec.: molecular ion at m/e 208.

7-Benzyloxy-5-Hydroxy-2,2-Dimethylchroman-4-one (XC)²⁴

5,7-Dihydroxychroman-4-one (XIV, 2 g., 0.01 mole) was dissolved in boiling acetone (100 ml.) with K_2CO_3 (1 g.). Benzyl bromide (1.4 ml., 0.01 mole) was added in two portions. The reaction mixture was refluxed for 3 hours. After filtering off K_2CO_3 , acetone was evaporated. Recrystallization of the residue from absolute alcohol gave colorless needles (2.8 g.) of 7-benzyloxy-5-hydroxy-2,2-dimethylchroman-4-one (95% yield), m. p. 133° (Lit.,²⁴ $133-4^\circ$).

The ir spectrum (KBr disc) showed the bands due to -OH at 3500 cm^{-1} (broad), and the carbonyl absorption at 1640 cm^{-1} (sharp).

The uv spectrum ($CHCl_3$) showed the max. at 243 and 295 $m\mu$; ϵ , 10,800 and 36,000.

Nmr (100 MHz, CCl_4): δ 1.42 (s, 6, gem-dimethyl), 2.54 (s, 2, methylene), 4.92 (s, 2, benzyl), 5.78-5.88 (q, 2, aryl), 6-7 (m, 1, phenoxy), and 7.18 (s, 5, benzyl aryl). [Fig. 2]

Mass Spec.: molecular ion at m/e 298.

7-Benzoyloxy-5-Methoxy-2,2-Dimethylchroman-4-one (XCI)²⁴

(i) To a solution of 7-benzoyloxy-5-hydroxychroman-4-one (XC, 2 g., 0.007 mole) in boiling acetone (100 ml.) with K_2CO_3 (1 g.), excess methyl iodide (6 ml.) was added. The reaction mixture was refluxed for 6 hours. After filtering off K_2CO_3 , acetone was evaporated. The residue was recrystallized from 95% alcohol which gave colorless rods (1.8 g.) of 7-benzoyloxy-5-methoxy-2,2-dimethylchroman-4-one (84% yield), m. p. 109-110° (Lit.,²⁴ 111°).

(ii) Diazomethane⁸⁸ (0.35 g.) in ether was added slowly at 0° to a solution of the chroman-4-one (XC, 2 g., 0.007 mole) in absolute alcohol (100 ml.). After stirring for 3 hours, the excess diazomethane was decomposed by glacial acetic acid. Most of the solvent was evaporated off. The residue was extracted with ether. Evaporation of the solvent gave only trace amount of the required product (XCI). Starting material was recovered.

(iii) Dimethyl sulfate (3 ml., 0.01 mole) was added to a solution of the chroman-4-one (XC, 2 g., 0.007 mole) in boiling acetone (100 ml.) with K_2CO_3 (2 g.). The reaction mixture was refluxed for 6 hours. After filtering off K_2CO_3 , acetone was evaporated. The residue was recrystallized from 95% alcohol which gave colorless rods (2 g.) of the required product (XCI) (95% yield).

The ir spectrum (KBr disc) showed the band due to the carbonyl absorption at 1690 cm^{-1} (sharp).

The uv spectrum (CHCl_3) showed the max. at 243 and 286 $\text{m}\mu$; ϵ , 10,600 and 43,900.

Nmr (100 MHz, CCl_4): δ 1.36 (s, 6, gem-dimethyl), 2.21 (s, 2, methylene), 3.68 (s, 3, methoxy), 4.90 (s, 2, benzyl), 5.84 (s, 2, aryl), and 7.19 (s, 5, benzyl aryl). [Fig. 3]

Mass Spec.: molecular ion at m/e 312.

10% Palladium-Charcoal Catalyst⁸⁹

Norit (5.7 g.) was heated on a steam-bath with 10% nitric acid for 2 hours. It was then washed free from acid with water, and dried at $100\text{-}110^\circ$ in oven. Palladium chloride (1 g.) was dissolved in conc. HCl (0.8 ml.) and water (5 ml.), and was heated on steam-bath until solution was complete. This solution was added to another solution of sodium acetate (22 g.) in water (125 ml.) in a 500 ml. reduction bottle. Charcoal was added, and the mixture was hydrogenated at 19 lb./sq. in. (1.1 atm.) pressure until no more absorption was observed. The catalyst was collected, washed with water (5 x 100 ml.) and sucked as dry as possible. After drying the catalyst at room temperature, it was dried over anhydrous CaCl_2 in a vacuum desiccator. Then the catalyst was stored in a tightly stoppered bottle and placed in a desiccator. About 6 g. of catalyst was obtained.

7-Hydroxy-5-Methoxy-2,2-Dimethylchroman-4-one (LII)²⁴

(i) 7-Benzyloxy-5-methoxychroman-4-one (XCI, 5g., 0.016 mole) dissolved in glacial acetic acid (200 ml.) with 10% Pd-C catalyst (0.5 g.) was effected with hydrogen at 40°, under 21 lb./sq. in. (1.2 atm.) pressure with a Parr Hydrogenation apparatus, until no more absorption was observed (about 300 ml. absorbed). After filtering off the catalyst, acetic acid was evaporated off by the rotavapor apparatus with steam-bath. The residue was recrystallized from absolute alcohol which gave colorless rectangular prisms (3 g.) of 7-hydroxy-5-methoxy-2,2-dimethylchroman-4-one (84% yield), m. p. 206-8° (Lit.,²⁴ 208-9°).

(ii) The chroman-4-one (XCI, 5 g., 0.016 mole) dissolved in absolute alcohol (150 ml.) with 10% Pd-C catalyst (2 g.) was effected with hydrogen (about 350 ml. absorbed) at 40°, under 21 lb./sq. in. (1.2 atm.) pressure. After filtering off the catalyst, the solvent was evaporated off. The residue was recrystallized from absolute alcohol which gave colorless rectangular prisms (2.5 g.) of the required product (LII) (70% yield).

The ir spectrum (KBr disc) showed the bands due to -OH at 3250 cm⁻¹ (broad), and the carbonyl absorption at 1680 cm⁻¹ (sharp).

The uv spectrum (CHCl_3) showed the max. at 243 and 284 $\text{m}\mu$; ϵ , 27,300 and 94,000.

Nmr (60 MHz, CDCl_3): δ 1.40 (s, 6, gem-dimethyl), 2.60 (s, 2, methylene), 3.80 (s, 3, methoxy), and 5.98 (s, 2, aryl).
[Fig. 4]

As mentioned earlier, these experiments were not always reproducible; other unsuccessful attempts included the following experiments:

(i) A mixture of the chroman-4-one (XCI, 1 g., 0.003 mole) in 84.5% phosphoric acid (15 ml.) and 90% formic acid (15 ml.) was refluxed at 110° for 2 hours.⁵⁸ The resulting orange solution was diluted with water. Orange precipitate formed was recrystallized from 95% alcohol. A mixture of the required product (LII) and phloroglucinol was obtained.

(ii) The chroman-4-one (XCI, 2 g., 0.006 mole) dissolved in conc. HCl (10 ml.) and alcohol (40 ml.) was refluxed for 2 hours.⁵⁷ The solvent was evaporated off. The residue was diluted with water (60 ml.) and neutralized with sodium bicarbonate. Extracted with ether, dried, and then evaporated off ether; the precipitate was recrystallized from 95% alcohol. Only phloroglucinol (0.5 g.), m. p. 218° was obtained.

When refluxing the chroman-4-one (XCI) in benzene with conc. HCl, the starting material was recovered.

When refluxing with a mixture of acetic acid and conc. HCl, a mixture of starting material and phloroglucinol was obtained. The same result was attained when refluxing the chroman-4-one (XCI) in solvent systems of benzene, alcohol with conc. HCl, or benzene, acetic acid with conc. HCl.

(iii) A few drops of conc. HCl was added to a solution of the chroman-4-one (XCI, 5 g., 0.016 mole) in glacial acetic acid (200 ml.) and was hydrogenated in the presence of 10% Pd-C catalyst (0.5 g.). No absorption was observed. A few drops of perchloric acid was added instead of HCl, but still no reaction was found.

(iv) A solution of the chroman-4-one (XCI, 5 g., 0.016 mole) in absolute alcohol (150 ml.) was hydrogenated in the presence of Adam's catalyst (0.2 g.) at room temperature at 21 lb./sq. in. (1.2 atm.) pressure (about 450 ml. absorbed). After filtering off the catalyst, alcohol was evaporated off. The residue was recrystallized from absolute alcohol. Only phloroglucinol was obtained.

Attempted Preparation of 7-Hydroxy-5-Methoxy-2,2-Dimethylchromane
(XCII)²⁴

A mixture of 7-hydroxy-5-methoxychroman-4-one (LII, 2 g., 0.009 mole), ethyl alcohol (20 ml.), 15% HCl (100 ml.) and amalgamated zinc dust⁹⁴ (80 g.) was kept for 2 days. Then

12% HCl (20 ml.) was added, and the reaction mixture was heated on steam-bath for 1 hour. After a further addition of 12% HCl (20 ml.), the reaction mixture was boiled for 6 hours. The product was isolated with ether. Dark oil was obtained instead of crystallized product.

7-Hydroxy-5-Methoxy-2,2-Dimethylchroman-4-ol (XCVI)

7-Hydroxy-5-methoxychroman-4-one (LII, 2 g., 0.009 mole) in anhydrous tetrahydrofuran (150 ml.) was heated with excess of lithium aluminium hydride (1 g.) under reflux for 6 hours. After treatment with dil. H_2SO_4 , the reaction mixture was evaporated at 70° to remove tetrahydrofuran. The residue was then extracted with ether, dried and evaporated. The precipitate was recrystallized from $CHCl_3$ which gave yellow crystals (1 g.) of 7-hydroxy-5-methoxy-2,2-dimethylchroman-4-ol (45% yield), m. p. 265° .

The ir spectrum (KBr disc) showed the band due to -OH absorption at 3500 cm^{-1} (broad).

The uv spectrum ($CHCl_3$) showed the max. at 246 and 283 m μ ; ϵ , 72,800 and 58,800.

Nmr (60 MHz, $CDCl_3$): 1.40 (s, 6, gem-dimethyl), 3.50 (d, 2, methylene), 3.85 (s, 3, methoxy), 4.60 (m, 1, α -H), 5.38 (m, 1, hydroxyl), and 6.10 (s, 2, aryl). [Fig. 5]

Before the successful preparation, an attempt with 7-hydroxy-5-methoxychroman-4-one (LII, 2 g., 0.009 mole) suspending in anhydrous ether (150 ml.), was heated with excess of lithium aluminium hydride (1 g.). The mixture was refluxed for 3 hours. After treatment with dil. H_2SO_4 , the ether layer was washed with water and aq. sodium bicarbonate solution, dried, and evaporated. The residue was recrystallized from $CHCl_3$, but only the starting material was recovered.

Attempted Dehydration of 7-Hydroxy-5-Methoxy-2,2-Dimethylchroman-4-ol

7-Hydroxy-5-methoxy-2,2-dimethylchroman-4-ol (XCVI, 1 g. 0.004 mole) was dissolved in benzene (50 ml.). *p*-Toluenesulfonic acid (0.1 g.) was added. The mixture was heated for 30 min. After cooling, the mixture was washed with water, extracted with ether, dried and evaporated. The residue was in form of brown oil, and no crystallizable product was obtained.

7-Acetoxy-5-Hydroxy-2,2-Dimethylchroman-4-one (C)

5,7-Dihydroxychroman-4-one (XIV, 2 g., 0.01 mole) was dissolved in acetic anhydride (5 ml.) with sodium acetate (2 g.) The reaction mixture was stirred at 40° for 3 hours. The excess acetic anhydride was decomposed with crushed ice. Acetic acid was neutralized with sodium bicarbonate solution. After extraction with ether, dried, and evaporated, the residue was recrystallized from very dilute aqueous alcohol which gave colorless crystals (1.8 g.) of 7-acetoxy-5-hydroxy-2,2-dimethylchroman-4-one (72% yield), m. p. 164°.

The ir spectrum (KBr disc) showed the bands due to the ester carbonyl absorption at 1760 cm⁻¹ (sharp), and the carbonyl absorption of the chroman-4-one at 1630 cm⁻¹ (sharp).

The uv spectrum (CHCl₃) showed the max. at 243 and 277 mμ; ε, 8,750 and 26,000.

Nmr (60 MHz, CDCl₃): δ 1.42 (s, 6, gem-dimethyl), 2.35 (s, 3, acetyl methyl), 2.58 (s, 2, methylene), and 6.05-6.15 (q, 2, aryl). [Fig. 6]

Attempted Methylation of 7-Acetoxy-5-Hydroxy-2,2-Dimethylchroman-4-one

7-Acetoxy-5-hydroxychroman-4-one (C, 2.5 g., 0.01 mole) was dissolved in boiling acetone (100 ml.) with K₂CO₃ (2 g.). Excess of methyl iodide (5 ml.) was added. The reaction mixture was refluxed for 6 hours. After filtering and evaporation, only oil remained.

5-Methoxy-7-(p-tolylsulfonyloxy)-2,2-Dimethylchroman-4-one
(CII)²⁷

A mixture of 5,7-dihydroxychroman-4-one (XIV, 4 g., 0.02 mole), K_2CO_3 (20 g.), p-tolylsulfonyl chloride (3.8 g., 0.02 mole; added in two lots at 30-min. intervals), and acetone (150 ml.) was refluxed for 5 hours. After cooling, more K_2CO_3 (20 g.) was added. Excess of methyl iodide (10 ml.) was added, and refluxing was continued for 16 hours. The mixture was filtered and evaporated to a crystalline residue, which was recrystallized from dilute methanol to give colorless crystals (2.4 g.) of 5-methoxy-7-(p-tolylsulfonyloxy)-2,2-dimethylchroman-4-one (30% yield), m. p. 152° (Lit.,²⁷ 152°).

The ir spectrum (KBr disc) showed the band due to the carbonyl and sulfonyl absorption at 1680 cm^{-1} (sharp).

The uv spectrum ($CHCl_3$) showed the max. at 240 and 274 m μ ; ϵ , 22,500 and 56,000.

Nmr (100 MHz, $CDCl_3$): δ 1.38 (s, 6, gem-dimethyl), 2.42 (s, 3, methyl), 2.60 (s, 2, methylene), 3.72 (s, 3, methoxy), 6.08-6.22 (q, 2, aryl), and 7.28-7.72 (q, 4, tolyl aryl). [Fig. 7]

5-Methoxy-7-(p-tolylsulfonyloxy)-2,2-Dimethylchroman-4-ol
(XXXI)²⁷

5-Methoxy-7-(p-tolylsulfonyloxy)chroman-4-one (CII, 2.4 g., 0.007 mole) was suspended in anhydrous ether (150 ml.) and heated with lithium aluminium hydride (1 g.). The mixture was refluxed for 4 hours. After treatment with dil. H₂SO₄, the ether layer was washed with water and aq. sodium bicarbonate solution, dried, and concentrated to a crystalline product, which was recrystallized from aq. methanol to give light yellow crystal (1.7 g.) of 5-methoxy-7-(p-tolylsulfonyloxy)-2,2-dimethylchroman-4-one (70% yield), m. p. 148° (Lit.,²⁷ 148°).

The ir spectrum (KBr disc) showed the bands due to -OH absorption at 3560 cm⁻¹ (sharp), and the sulfonyl absorption at 1680 cm⁻¹ (sharp).

The uv spectrum (CHCl₃) showed the max. at 246 and 283 mμ; ε, 72,800 and 58,800.

Nmr (60 MHz, CDCl₃): δ 1.36 (d, 6, gem-dimethyl), 1.95-2.05 (d, 2, methylene), 2.45 (s, 3, methyl), 3.25 (s, 1, hydroxyl), 3.80 (s, 3, methoxy), 4.90-5.10 (t, 1, α-H), 6.15-6.40 (m, 2, aryl), and 7.40-7.90 (q, 4, tolyl aryl). [Fig. 8]

5-Methoxy-7-(p-tolylsulfonyloxy)-2,2-Dimethylchromene

(XXXII)²⁷

A mixture of the chroman-4-ol (XXXI, 1.7 g., 0.005 mole), toluene (80 ml.), and p-toluenesulfonic acid (0.1 g.) was refluxed slowly for 15 min. The orange solution was cooled, washed with water, dried, and evaporated to dryness under reduced pressure. The residue was recrystallized from methanol to give yellow plates (0.9 g.) of 5-methoxy-7-(p-tolylsulfonyloxy)-2,2-dimethylchromene (60% yield), m. p. 98° (Lit.,²⁷ 98°).

The ir spectrum (KBr disc) showed the band due to sulfonyl absorption at 1680 cm^{-1} (sharp).

The uv spectrum (CHCl_3) showed the max. at 243 and 279 m μ ; ϵ , 21,400 and 30,300.

Nmr (60 MHz, CDCl_3): δ 1.35 (s, 6, gem-dimethyl), 2.45 (s, 3, methyl), 3.72 (s, 3, methoxy), 5.50-5.68 and 6.58-6.75 (2d, 2, vinyl, $J = 10$ cps), 6.10-6.35 (m, 2, aryl), and 7.40-7.95 (q, 4, tolyl aryl). [Fig. 9]

7-Hydroxy-5-Methoxy-2,2-Dimethylchromene (XCVII)²⁷

A solution of potassium hydroxide (3 g.) in water (50 ml.) and alcohol (50 ml.) was prepared. The alkaline solution was added to the chromene (XXXII, 0.9 g., 0.003 mole) in three 30-ml. portions at 15-min. intervals. After refluxing for 1 hour, the solution was cooled, neutralized with acetic acid, and concentrated at 50° under diminished pressure. The mixture was extracted with ether and the extract was washed successively with aq. sodium bicarbonate and 3% aq. sodium hydroxide solutions. The sodium hydroxide portion was saturated with carbon dioxide (dry ice) and the precipitate was recrystallized from aq. methanol. A mixture of the chromene (XCVII) and *p*-toluenesulfonic acid was obtained. After purification through column chromatography (silica gel), yellow plates (0.2 g.) of 7-hydroxy-5-methoxy-2,2-dimethylchromene (45% yield), m. p. 188° was obtained. The *p*-toluenesulfonic acid was recrystallized from acetone in rectangular prisms, m. p. 104°.

The ir spectrum (KBr disc) of the chromene (XCVII) showed the band due to the phenoxy absorption at 3500 cm⁻¹ (broad).

The ir spectrum (KBr disc) of *p*-toluenesulfonic acid showed the band due to the sulfonyl absorption at 1670 cm⁻¹ (sharp).

The uv spectrum (CHCl_3) showed the max. at $245 \text{ m}\mu$;
 ϵ , 46,400.

Attempted Preparation of Alloxanthoxyletin (V)

7-Hydroxy-5-methoxychromene (XCVII, 2 g., 0.012 mole) was added to a mixture of malic acid (2.2 g., 0.02 mole) in 73% H_2SO_4 (100 ml.). The reaction mixture was stirred at 40° for 6 hours, and then was poured onto crushed ice. Dark brown precipitate formed which was recrystallized from aqueous methanol. Only the starting material was recovered.

The above experiment was repeated by using conc. H_2SO_4 instead. Dark oil was produced. No crystallizable product was obtained.

The fore experiment was repeated with 73% H_2SO_4 , refluxing at 80° . Brown precipitate formed, was recrystallized from aq. alcohol. Still no required product (V) was obtained.

6,7-Dihydro-6,6-Dimethyl-9-Hydroxy-8-Oxo-Pyrano [2.3-f] -
Coumarin (LXXXV)

5,7-Dihydroxychroman-4-one (XIV, 4 g., 0.02 mole) was added to a mixture of malic acid (2.2 g., 0.02 mole) and 73% H_2SO_4 (150 ml.). The reaction mixture was stirred at 40° for 3 hours, and then poured onto crushed ice. The yellow precipitate which recrystallized from aqueous alcohol gave yellow crystals (2 g.) of 6,7-dihydro-6,6-dimethyl-9-hydroxy-8-oxo-pyrano [2.3-f] coumarin (39% yield), m. p. 220° (Lit.,⁸ 220°).

The ir spectrum (KBr disc) showed the bands due to the lactone absorption at 1720 cm^{-1} (sharp), and the carbonyl absorption at 1640 cm^{-1} (sharp).

The uv spectrum ($CHCl_3$) showed the max. at 240, 285 & 328 $m\mu$; ϵ , 5,240, 18,300 and 7,980 respectively.

Nmr (60 MHz, $CDCl_3$): δ 1.66 (s, 6, gem-dimethyl), 3.00 (s, 2, methylene), 6.40-6.60 and 8.25-8.40 (2d, 2, vinyl, $J = 10\text{ cps}$), and 6.72 (s, 1, aryl). [Fig. 10]

6,7-Dihydro-6,6-Dimethyl-9-Methoxy-8-Oxo-Pyrano [2.3-f]-
Coumarin (LXXXVI)

9-Hydroxy-coumarin (LXXXV, 1 g., 0.004 mole) was dissolved in boiling acetone (100 ml.) with K_2CO_3 (1 g.). Excess of methyl iodide (2 ml.) was added. The reaction mixture was refluxed for 8 hours. After filtering and evaporation of acetone, the residue was recrystallized from acetone to give colorless crystals (0.5 g.) of 6,7-dihydro-6,6-dimethyl-9-methoxy-8-oxo-pyrano [2.3-f] coumarin (35% yield), m. p. $193-4^\circ$ (Lit.,⁸ 193°).

The ir spectrum (KBr disc) showed the bands due to the lactone absorption at 1720 cm^{-1} (sharp), and the carbonyl absorption at 1680 cm^{-1} (sharp).

The uv spectrum ($CHCl_3$) showed the max. at 239, 277 and $328\text{ m}\mu$; ϵ , 5,780, 17,500 and 8,960.

Nmr (60 MHz, $CDCl_3$): δ 1.47 (s, 6, gem-dimethyl), 2.70 (s, 2, methylene), 3.88 (s, 3, methoxy), 5.59-6.14 and 7.74-7.90 (2d, 2, vinyl), and 6.27 (s, 1, aryl). [Fig. 11]

Attempted Reduction of Compound (LXXXVI)⁸

9-Methoxy-coumarin (LXXXVI, 1 g., 0.004 mole) dissolved in pyridine (15 ml.) and water (5 ml.) was treated dropwise with a solution of NaBH_4 (0.5 g.) in water (5 ml.). The reaction mixture was heated at 70° for 1 hour, cooled and acidified with 2N HCl. It was thoroughly extracted with CH_2Cl_2 . The CH_2Cl_2 extract was successively washed with dil. HCl, 5% NaHCO_3 , and water, and then dried over Na_2SO_4 . Removal of the solvent gave a mixture, with most of the starting material recovered.

Phloroglucinaldehyde⁷³

Into a solution of anhydrous phloroglucinol (4 g., 0.032 mole) in dry ether (25 ml.) containing $\text{Zn}(\text{CN})_2$ (2 g.) in an ice-bath, a good stream of dry HCl ⁹⁵ was passed until the oil formed solidified. After standing for 2 hours, the yellow solid was collected and washed with ether. The imide salt was then dissolved in water (60 ml.), and hydrolysed for 15 min. at room temperature. The solid obtained on cooling was collected. Yellow needles (2 g.) of phloroglucinaldehyde (58% yield) which decomposed around 200° was obtained.

Aqueous solution of the product gave red coloration with ferric chloride (test for phloroglucinaldehyde). Its 2,4-dinitrophenylhydrazone (orange precipitate) decomposed around 300° .

5,7-Dihydroxycoumarin (CVI)

Phloroglucinol (5 g., 0.04 mole) was added to a solution of malic acid (4.5 g., 0.04 mole) in 73% H_2SO_4 (100 ml.). The reaction mixture was stirred at 40° for 6 hours, and then was poured onto crushed ice. Yellow precipitate was obtained which was recrystallized from aq. alcohol to give yellow needles (3 g.) of 5,7-dihydroxycoumarin (43% yield), m. p. 290° .

The ir spectrum (KBr disc) showed the bands due to the lactone absorption at 1760 cm^{-1} and 1720 cm^{-1} (sharp), and the phenoxy absorption at 3440 cm^{-1} (broad).

The uv spectrum ($CHCl_3$) showed the max. at $327\text{ m}\mu$; ϵ , 26,700.

Before the successful preparation, an attempt with phloroglucinaldehyde (2 g., 0.018 mole) was tried. The phloroglucinaldehyde was dissolved in 10% NaOH solution (25 ml.). A solution of cyanoacetic acid⁹⁶ (1.75 g., 0.02 mole) in alcohol (6 ml.) was added. The reaction mixture was agitated for 24 hours. The solution was acidified with HCl, but no precipitate deposited. The solution was then extracted with ether. After evaporation of ether, only brown oil remained.

7-Methoxy-5-Hydroxycoumarin (CVII)

5,7-Dihydroxycoumarin (CVI, 3 g., 0.02 mole) was dissolved in boiling acetone (150 ml.) with K_2CO_3 (2 g.). Methyl iodide (1 ml., 0.02 mole) was added. The reaction mixture was refluxed for 3 hours. The mixture was filtered and evaporated. The residue that recrystallized from aqueous alcohol gave yellow crystals (1.5 g.) of 7-methoxy-5-hydroxycoumarin (40% yield), which decomposed at 220° .

The ir spectrum (KBr disc) showed the bands due to the lactone absorption at 1760 cm^{-1} and 1730 cm^{-1} (sharp), and the phenoxy absorption at 3500 cm^{-1} (broad).

The uv spectrum ($CHCl_3$) showed the max. at $327\text{ m}\mu$; ϵ , 30,720.

3,3-Dimethylallyl Alcohol (CVIII)^{47c}

3,3-Dimethylacrylic acid (25 g., 0.25 mole) in dry ether (100 ml.) was added dropwise during 2 hours to a stirred slurry of lithium aluminium hydride (10 g.) in ether (250 ml.) at 0°. After 24 hours at room temperature, water (30 ml.) was added, followed by dil. H₂SO₄. The ether layer was separated, washed with aq. sodium bicarbonate solution, and dried. Evaporation of ether gave a residue which upon distillation gave a colorless liquid (10 g.) of 3,3-dimethylallyl alcohol (43% yield), b. p. 138° (Lit.,^{47c} 140°/764 mm.).

3-Methylbut-2-enal (CIX)^{47c}

3,3-Dimethylallyl alcohol (CVIII, 10 g., 0.12 mole) in methylene dichloride (400 ml.) was shaken with active manganese dioxide (70 g.) for 24 hours. The solid was removed, and washed with methylene chloride. The filtrate and washings were combined, dried and evaporated. The residue was distilled to yield a yellow liquid (6 g.) of 3-methylbut-2-enal (60% yield), b. p. 120-130° (Lit.,^{47c} 123-8°/764 mm.).

Attempted Dimethylchromenylation of 5-Hydroxy-7-Methoxy-
Coumarin (CVII)

To a stirred mixture of 5-hydroxy-7-methoxycoumarin (CVII, 1.5 g., 0.008 mole) and dry pyridine (3 g.), 3-methylbut-2-enal (1.5 g., 0.01 mole) was added at 140°. The heating was continued for 8 hours. The mixture was evaporated to dryness, and the residue was chromatographed on silica gel. Only the starting material was recovered.

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