Chapter II

Synthesis of Furobenzopyrones by Claisen Rearrangement

INTRODUCTION

Furocoumarins or furobenzo-α-pyrones, form a class of compounds, which occur in nature. They are found mainly in the plants of psoralea corylifolia, xanthylum flavum, angelica archangelic and bergamot fruit. These furocoumarins can also be prepared by starting with suitably substituted coumarin derivatives and then building up furan ring over it or by building up pyrone ring on hydroxy benzofurans.

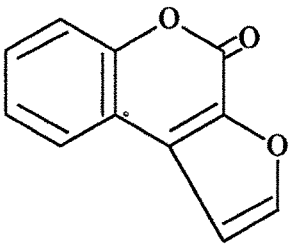
Comprehensive reviews about the chemistry of naturally occurring coumarins by Spath[1], Dean[2,3], Reppel[4] and furocoumarins by Karrer[5] are reported in the literature.

Naturally occurring furocoumarins often possess varied physiological activities. The role of certain plant juices and extractions containing furocoumarins for the treatment of skin lesions such as vitiligo has been known for many years. Juices of various parts of the plants e.g. parsley, celery, fig and parsnip after contact with the skin and exposure to sunlight cause changes on mammalian skin manifested by erythema and increased pigmentation. The discovery of this unique activity of furocoumarins stimulated the research in this area. These are also widely utilized for the treatment of hyperproliferative skin diseases as chemical probes for chromatin structure[6,7] and more recently, in the treatment of human immunodeficiency disease (AIDS)[8].

PHYSIOLOGICAL ACTIVITIES

Eight different isomeric forms of furocoumarins (1-8) are reported in the literature. Out of them only two, furo(3,2-g)benzopyran-7H-one and furo(2,3-h) benzopyran-5H-one are found to occur in nature. These are commonly known as psoralen (6) and angelicin (7) respectively. The other six isomers do not occur in nature but are synthesized.

Linear furocoumarins, psoralens are found to possess remarkable skin photosensitizing activity causing phytophotodermatitis[9,10]. Some linear



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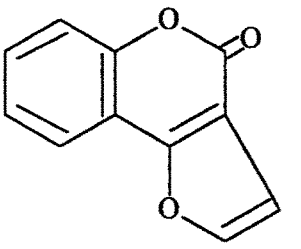

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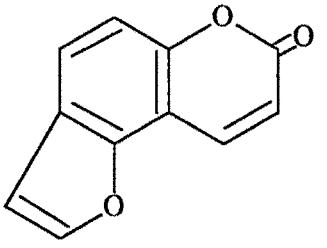

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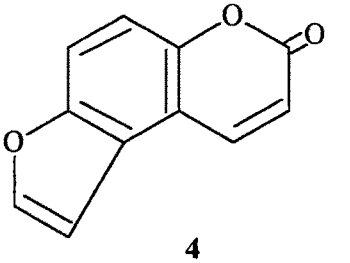

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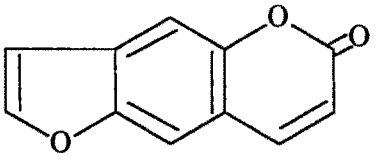

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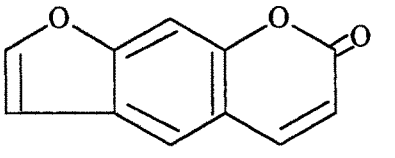

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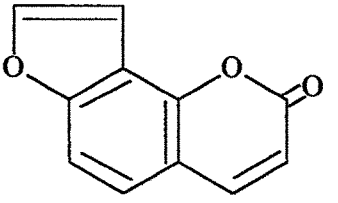

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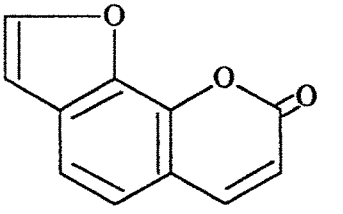

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furocoumarins are psoralen (6), 5-methoxypsoralen (5-MOP or bergapton) (9), 8-methoxypsoralen (8-MOP or xanthotoxin) (10) and 4,5′,8-trimethylpsoralen (TMP) (11). These are widely used in PUV-A (Psoralen UltraViolet-A) therapy for the treatment of dermatological disorders like psoriasis[11], vitiligo[12], atropic eczema[13] and micosis fungoides[14] in tumor stage. They are also known to be phototoxic to insects, fungi, viruses and bacteria[15-20].

However, 8-MOP or xanthotoxin is currently the only PUV-A drug in general clinical use, but it produces some unwarranted side effects in patients[21]. Furthermore, 8-MOP in combination with UV-A irradiation has moderate mutagenic properties[22,23] and found to be carcinogenic in mice[24,25].

Saied *et al.*[26] investigated the choice of the suitable drug for topical applications, with appropriate dosage, percutaneous permeation of the psoralen in connection with their solubilities and partition coefficients in octanol/water system and observed that epidermis were in the order of 8-MOP>5-MOP> TMP. Thus TMP could be considered as the most convenient psoralen for topical applications, because of weak penetrability.

STRUCTURE ACTIVITY RELATIONSHIP

Kuske[27] revealed in his early studies that certain furocoumarins are active agents responsible for the photodermatitis at 334-366nm, while Musajo *et al.*[28,29] from their extensive studies found the relation between the structure and photodynamic behaviour and established that under solar or 365nm UV-radiation, psoralen shows the highest activity among the natural coumarins followed up by decreasing order 8-MOP (10), 5-MOP (9) and angelicin (7).

It has been reported that the linear furan ring fused to benzopyrone system was necessary for the photosensitizing activity, whereas the angular furocoumarin exerts little activity and the introduction of hydroxyl group at position 5 and 8 or both becomes inactive, although activity is restored by methylation of either but not both of these hydroxyl groups. Pathak and his

associates[30] observed that methyl substitution at 4,5′ or 8 did not reduce the activity but was lowered by introducing methyl groups at 3 or 4′ positions.

Marley and coworkers[31] suggested that psoralen and 8-MOP are quite susceptible to photolysis in polar solvents like water, liberating many cleavage products including aldehydes, carboxylic acids and hydrogen peroxide, found to be toxic, even in the absence of light.

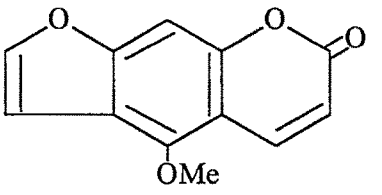
MODE OF ACTION

Psoralen (6), 8-MOP (10), TMP (11) and 3-carboethoxypsoralen (12) are some photodynamically active furocoumarins known for photochemotherapy. Although these are stable in dark, they undergo modification by UV-A irradiation. These can act through two mechanisms: [i] the drug, on absorption of light quanta in uv-visible region is promoted to the electronically excited singlet state, which may decay to ground state by emitting the radiation through radiative or non-radiative pathways or [ii] it can be converted to triplet excited state, having a longer life time and greater intrinsic activity. Triplet state can also decay to ground state in the same way.

Thomas and Alan[32] studied zero field splitting parameters (D^*) of various furocoumarins in the triplet state using an optically detected NMR and explained the inactivity of 8-hydroxypsoralen (13) as skin sensitizer. This is due to its anomalous large zero field splitting parameter (D^*).

In this, the photoactive psoralen or furocoumarin prior to exposure to the UV-irradiation becomes loosely associated within the DNA strand of epidermal and dermal cells. When these loosely bound psoralen molecules are photoactivated by UV-A (320-400nm) irradiation, they form covalent chemical bonds with thyamine bases of DNA (monofunctional adducts). The photoaddition involves the formation of cyclobutane bridge between the 5,6 double bond of a base and 3,4 or 4′,5′ double bond of the psoralen **14A, 14B**.

The first photochemical reaction is usually the addition of 4′,5′ double bond of furan ring with 5,6 double bond of thyamine. This results in the



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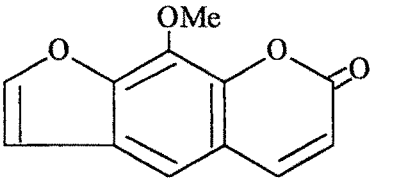

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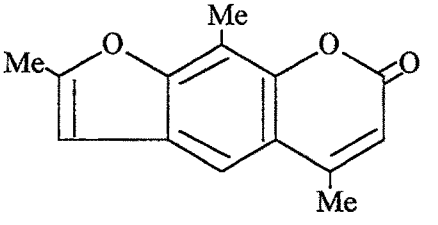

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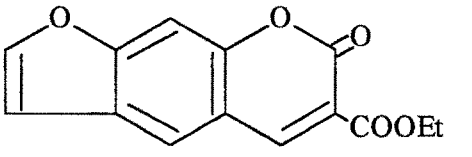

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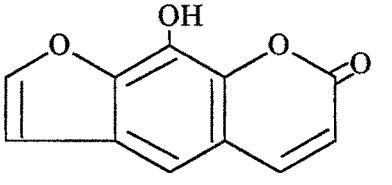

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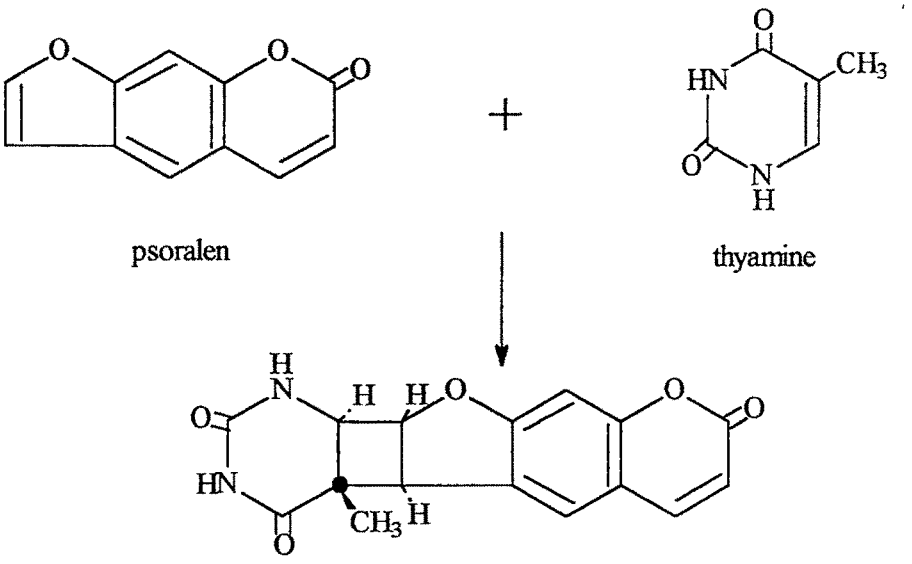
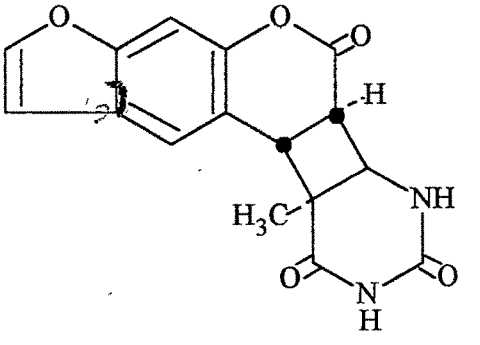


psoralen + thyamine

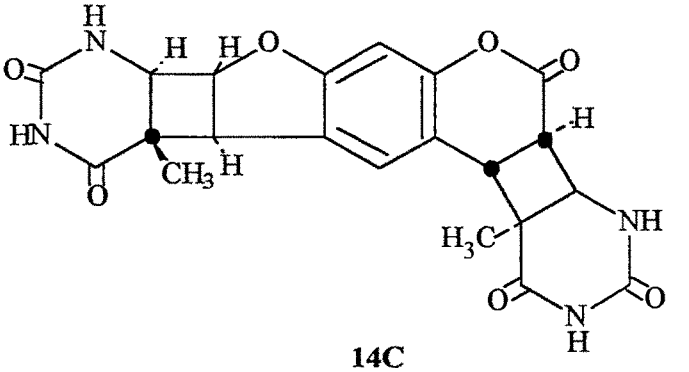
14A

addition across the 4',5'-double bond



14B

addition across the 3,4-double bond



14C

diadduct

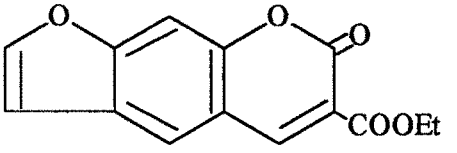
formation of fluorescent adduct, which absorbs at 360nm. Subsequent absorption of a second photon by the mono adduct leads to the formation of additional covalent linkage between the 3,4 double bond of pyrone with the thyamine of the opposite strand **14C**, thus cross-linking the two strands of the double helix. The capacity of various furocoumarins to form interstrand cross-linkages is different. The repair of these linkages is much less effective than repair of monoadducts, which finally leads into antiproliferative, mutagenic and photocarcinogenic effect or alteration of the immune system.

As a consequence of this, the development of monofunctional furocoumarins which express a high photobinding capacity towards DNA but reduced mutagenic and carcinogenic activity[33] are of present importance. Monofunctional compounds 3-carboethoxypsoralen (15), pyridopsoralen (16), 4,4′-dimethylangelicin (17), 4,5′-dimethylangelicin (18) and 6,4′-dimethyl-angelicin (19) are now widely used for therapeutical treatment as they do not form interstrand photocross-links inside duplex DNA due to steric hindrance.

The above introduction describes the information pertaining to furocoumarin's, relative activity, structural relationship and mode of action. Now different conventional and recent approaches for linear as well as angular furobenzopyrones will be discussed and more emphasis is being given to the monofunctional furocoumarins as they are of more interest due to their favourable properties.

DIFFERENT APPROACHES FOR THE SYNTHESIS OF FUROBENZOPYRONES

Psoralen and angelicin occupy a prominent position due to their physiological and therapeutic behaviour. There are many methods described in the literature. The following are some of the important methods to synthesize furocoumarins and their derivatives.



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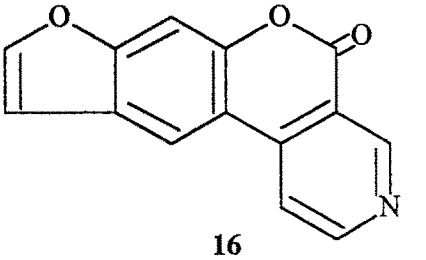

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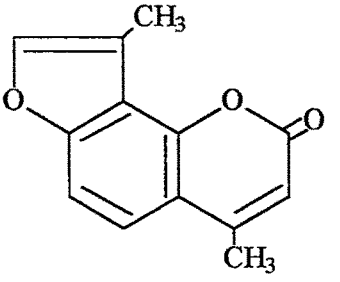

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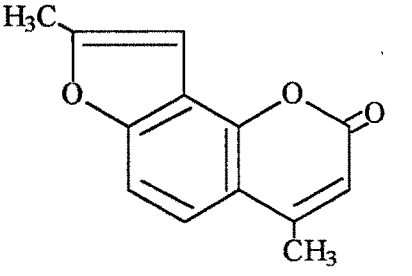

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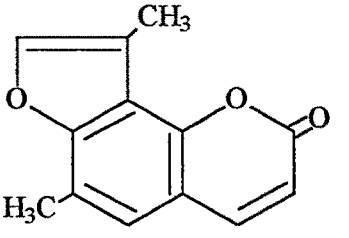

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Psoralen can be prepared by two alternative routes: [i] from 6-hydroxy coumaran (20) or [ii] through umbelliferone (21), using resorcinol as starting material. **[Scheme II.1]**

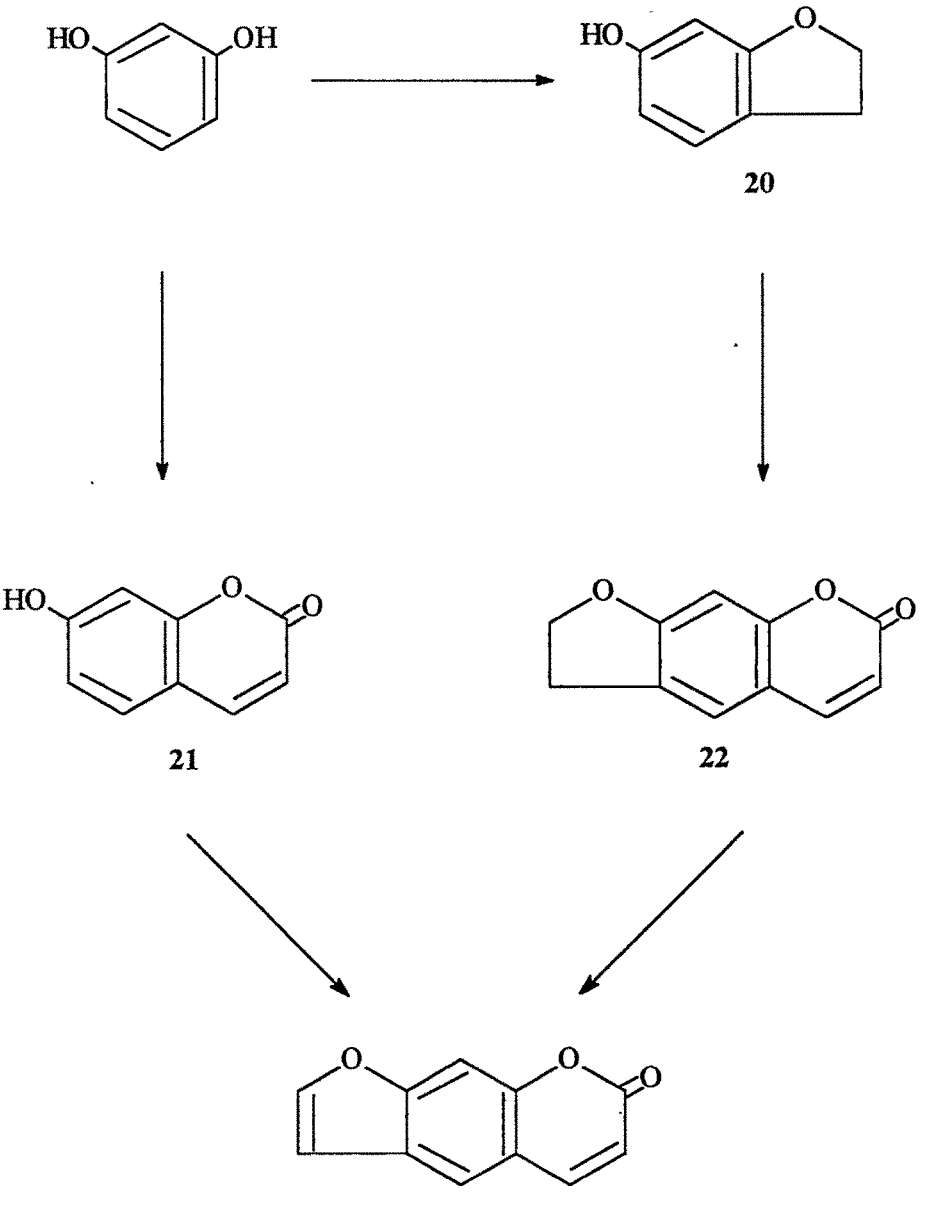
Spath and Pailer[34] carried out the condensation of 6-hydroxy coumaran (20) with malic acid in the presence of conc. H_2SO_4 to obtain 2,3-dihydropsoralen (22), which on dehydrogenation with Pd/C gave psoralen (6). **[Scheme II.2]** Later Horning and Reisner[35] prepared different 5-substituted 2,3-dihydropsoralen derivatives by condensing 6-acetoxy coumaran (23) with a variety of β-ketonic ester in the presence of conc. H_2SO_4. Esse and Chistenson[36] extended this reaction to get 6-alkyl-2,3-dihydro-5-methylpsoralen by condensing appropriate α-alkyl-β-ketonic esters with 6-acetoxycoumaran. The main drawback in the method is final dehydrogenation of dihydropsoralen derivatives **24** with Pd/C, which give poor yields of psoralen derivatives **25**. **[Scheme II.3]**

Later Chatterjee and Sen[37] synthesized the same psoralen and 3-methyl psoralen in a relatively good yield using 6-acetoxycoumaran (23), which on condensation with acrylonitrile and zinc chloride in dry HCl gas furnished 2,3,5,6-tetrahydropsoralen (26), followed by dehydrogenation with Pd/C. **[Scheme II.4]**

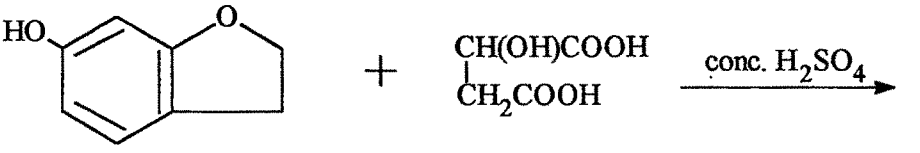
Rodighiero and Antonello[38] synthesized xanthotoxin (10) by first preparing 7-hydroxy-8-methoxy-6-formylcoumarin (27) and then condensing it with ethylbromoacetate to give corresponding ether **28**, which was hydrolyzed and subjected to cyclization with sodium acetate and acetic anhydride to give xanthotoxin (10). **[Scheme II.5]**

Seshadri and his colleague[39] synthesized psoralen using an indirect method by carrying out the thermal rearrangement of 4-allyloxy-2-methoxybenzaldehyde (29) with anhydrous $AlCl_3$ at 220°C to obtain 5-allyl-2,4-dihydroxybenzaldehyde (30), which was then subjected to Perkin reaction

Scheme II.1



Scheme II.2



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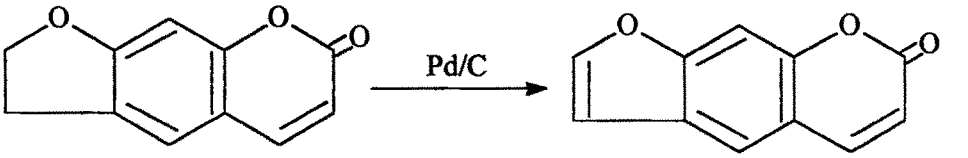

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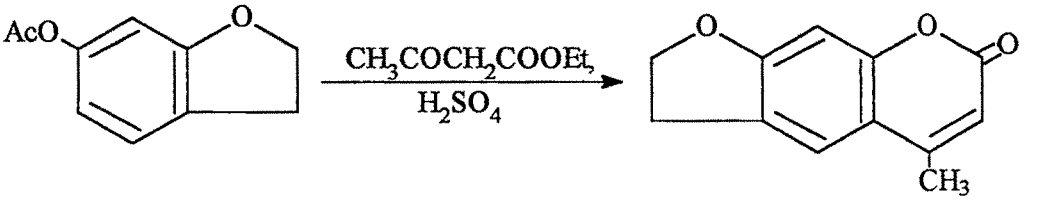
Scheme II.3



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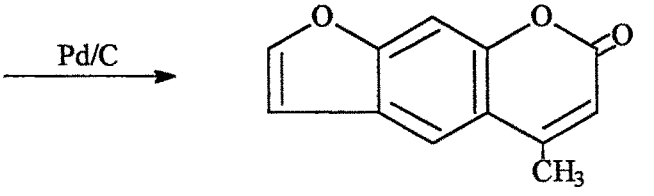

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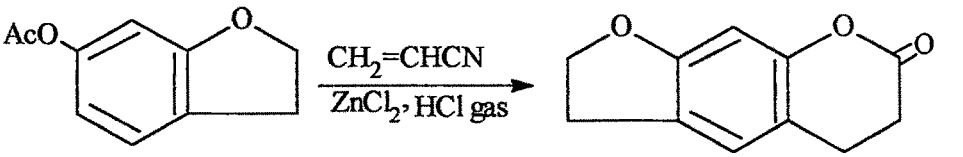
Scheme II.4



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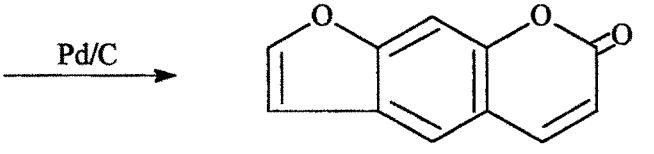


to obtain the coumarin derivative **31** followed by ozonolysis and cyclization to give psoralen. **[Scheme II.6]**

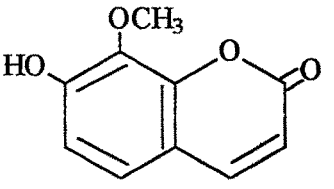
However, Ray *et al.*[40] achieved the synthesis of key compound 6-allyl coumarin for making psoralen from resorcinol in four steps by condensing resorcinol and acrylonitrile in the presence of $ZnCl_2$ to obtain 7-hydroxy-3,4-dihydrocoumarin (32). Allylation of **32** afforded allyloxy derivative **33**, followed by Claisen rearrangement gave 6-allyl-7-hydroxy-3,4-dihydro coumarin (34), which on subsequent dehydrogenation furnished 6-allyl-7-hydroxycoumarin (31). **[Scheme II.7]**

Hayakawa and coworkers[41] synthesized psoralen and azapsoralen from readily prepared trans-1-(phenylsulfinyl)-1-hepten-6-yn-3-one (35) with furan on acid-catalyzed reaction to get **36**, which underwent thermal cyclization to form neopentylacetal (37). This on heating with Pd/C in xylene yielded **38** as major product, which was then converted into tricyclic ketone **39** followed by Bayer-Villiger oxidation and subsequent dehydrogenation with Pd/C furnished psoralen in 28% yield. Whereas, azapsoralen (41) was prepared by treating hydroxylaminehydrochloride to give **40**, followed by mesylation, Backmann rearrangement and dehydrogenation with Pd/C to yield **41**. **[Scheme II.8]**

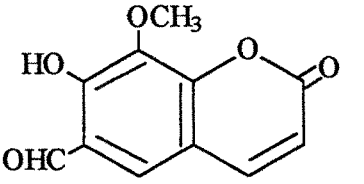
The important biological properties and moderate yields in conventional routes made Zubia *et al.*[42] to think for a different synthetic route. They finally achieved the synthesis of furocoumarins in greater yields adopting an alternative approach by coupling an acetylenic reagent with an o-iodohydroxycoumarin (44). The key iodination step of umbelliferone (21) at position 6 to prepare psoralen was made possible by following the strategy in which the lactone ring gets opened to give **42** followed by iodination produce **43** in order to modify the regioselectivity, otherwise the iodination on **21** goes to 8^{th} position which yields angelicin. **[Scheme II.9]**

Antonello and coworkers[43] synthesized three new psoralens **47a-c** with methyl groups from corresponding 7-hydroxycoumarins **45a-c** by cyclizing acetonyl derivatives **46a-c** in alkaline medium. These methyl substituted

Scheme II.5



DMF, $POCl_3$



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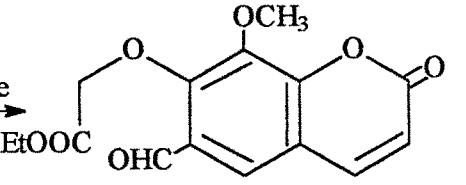
Ethylbromoacetate



i) NaOH

ii) Ac_2O/NaOAc

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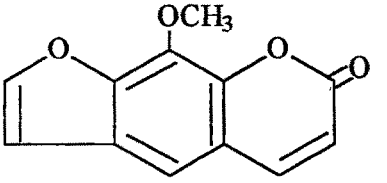

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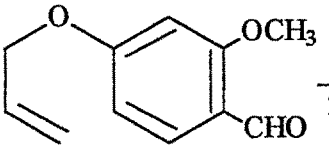
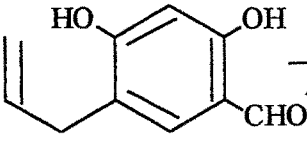
Scheme II.6

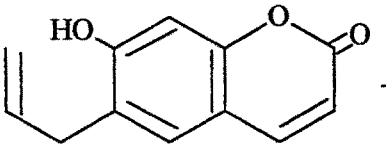


$AlCl_3$, 220°C, Δ



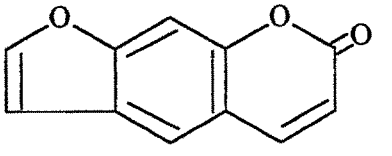
NaOAc/ Ac_2O, 170°C

29 **30**



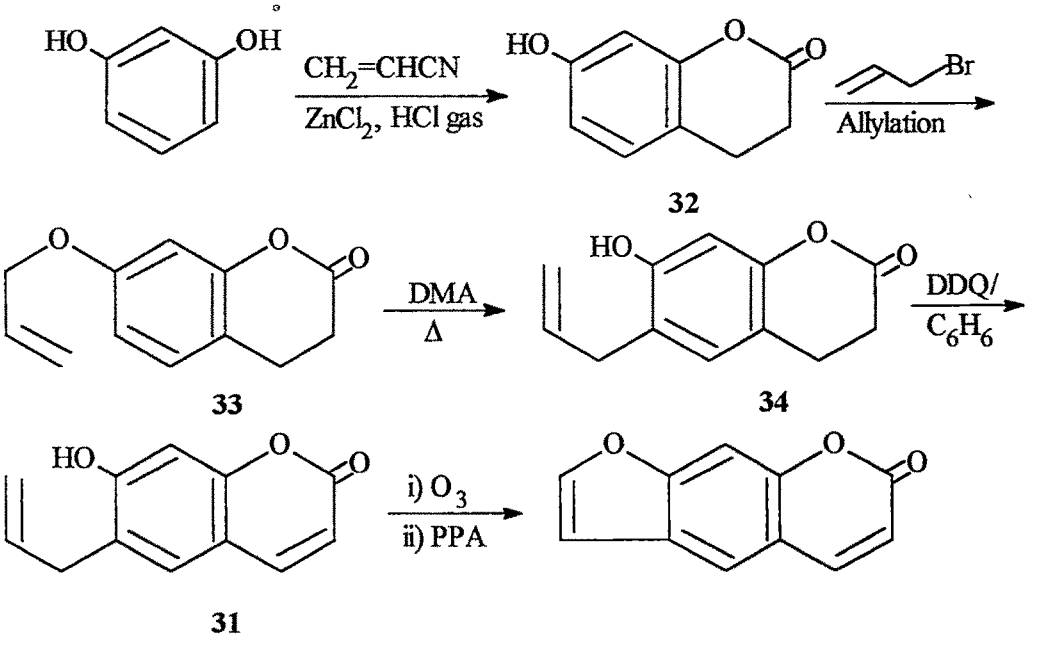
i) O_3

ii) PPA

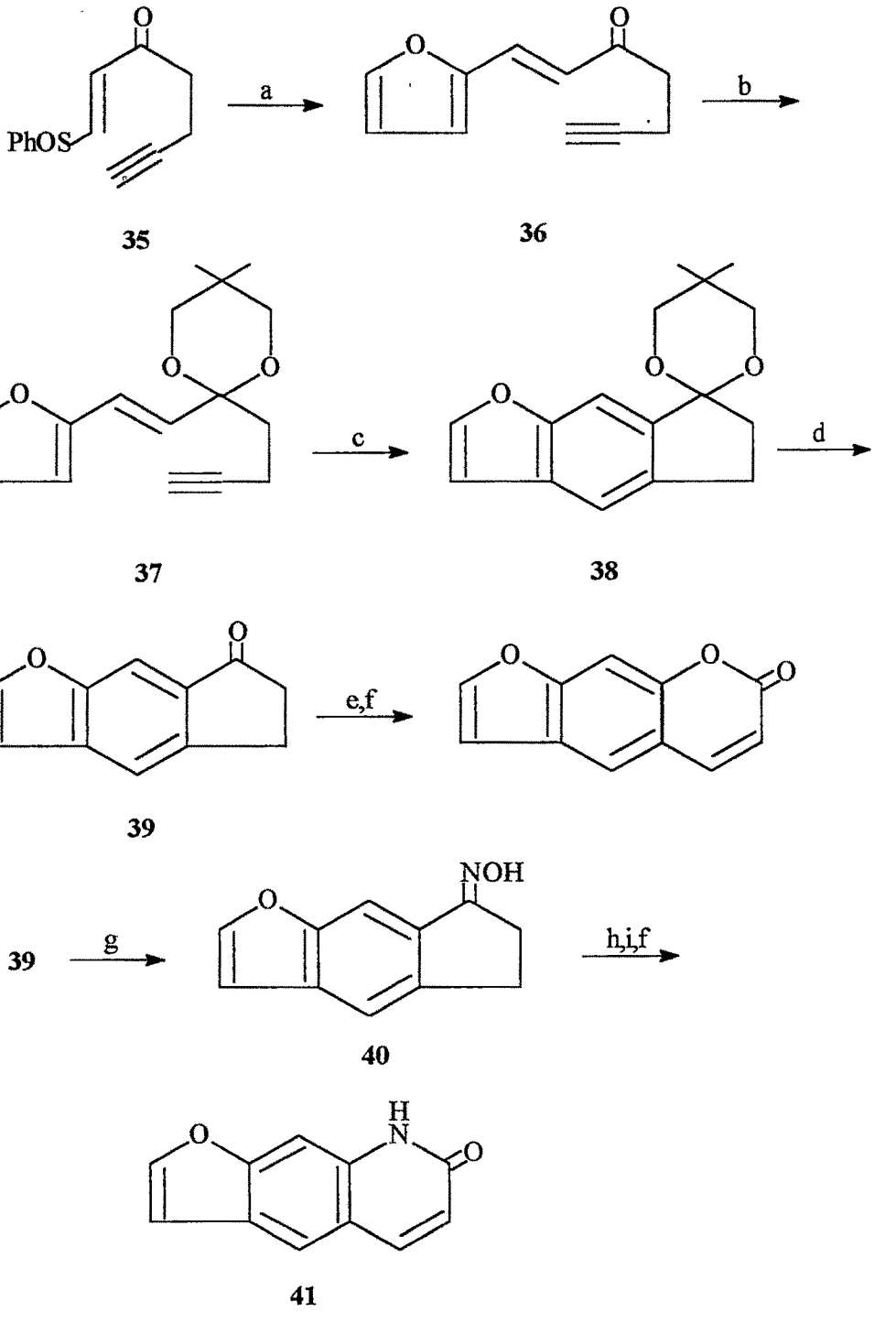


31

Scheme II.7


HO
OH
CH_2=CHCN
$ZnCl_2$, HCl gas
HO
O
O
Br
Allylation
32
O
O
O
DMA
Δ
HO
O
O
DDQ/
C_6H_6
33
34
HO
O
O
i) O_3
ii) PPA
O
O
O
31

Scheme II.8



(a) furan, p-TsOH; (b) $Me_2C(CH_2OH)_2$, p-TsOH, benzene, Δ; (c) Pd/C, xylene, (d) p-TsOH, THF, H_2O; (e) H_2O_2, Ac_2O, H_2SO_4, CH_2Cl_2; (f) Pd/C, DPE, Δ; (g) $NH_2OH.HCl$, NaOAc, EtOH; (h) MsCl,Et_3N,CH_2Cl_2 ; (i) Et_2AlCl,CH_2Cl_2 , -70 °C

psoralens are reported to exhibit considerable interaction with DNA, good photoreactivity against the macromolecule as well as antiproliferative activity. **[Scheme II.10]**

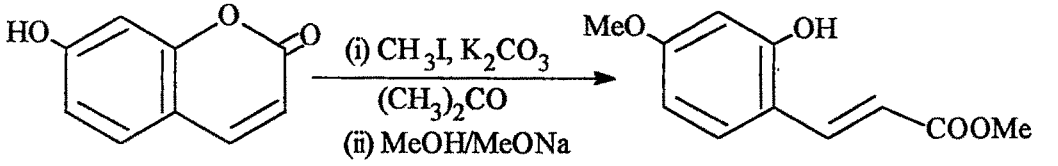
Kobayashi *et al.*[44] synthesized several furocoumarins and furochromones by 2+2 photoaddition between enolised 1,3-dicarbonyl compounds, such as 4-hydroxycoumarin and alkenes, followed by a β-scission of the cyclobutanoxyl radicals derived from the resulting cyclobutanols[45-47]. The radical fragmentations were found to take place regioselectively and result in a transformation of the cyclobutane rings into furan rings by incorporation of the alkoxy oxygen. Thus, 2+2 photoaddition of 4-hydroxy/acetoxycoumarins **48** formed cyclobutanols **49**, which were transformed into respective furocoumarins **50** and/or furochromones **51**. **[Scheme II.11]**

All the above methods focussed mainly on different approaches for the synthesis of psoralen and its derivatives. However, from the extensive studies it was understood, these type of compounds cause some side effects on application in PUV-A treatment due to their cross-linking ability with DNA. Since then research work was modified to prepare compounds so as to form mono adduct with DNA to minimize side effects. Angelicin which has angular structure hitherto considered inactive was studied and found to form mono adducts and capable of improving photochemotherapy of psoriasis. The other potential monofunctional compounds syntheses are also discussed.

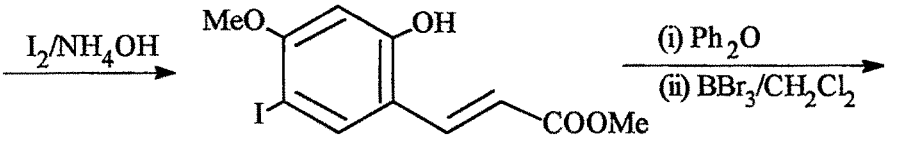
Angelicin is also a naturally occurring furocoumarin and was synthesized first by Spath and Pailer[48] by the condensation of sodium salt of 8-formylumbelliferone (52) with iodoaceticester followed by decarboxylative cyclization of corresponding ether **53** with sodium acetate and acetic anhydride to obtain angelicin (7), however the yields reported were very poor. **[Scheme II.12]**

Aneja *et al.*[49] synthesized angelicin in good yield from Claisen rearrangement of 7-allyloxycoumarin (54) to 7-hydroxy-8-allylcoumarin (55).

Scheme II.9



21 42



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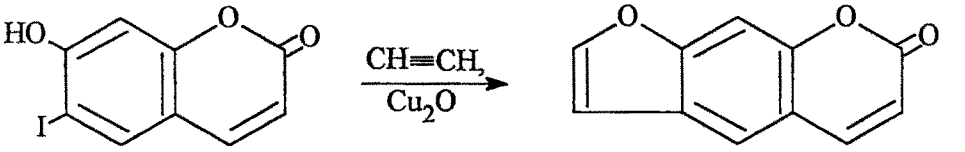
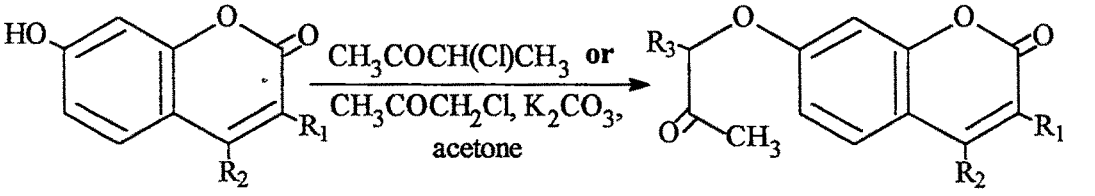


44

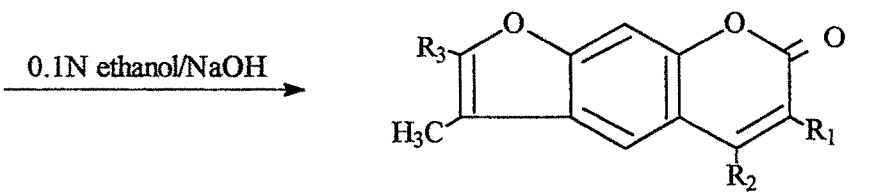
Scheme II.10



45 46

	R_1	R_2
a	H	H
b	CH_3	H
c	CH_3	CH_3

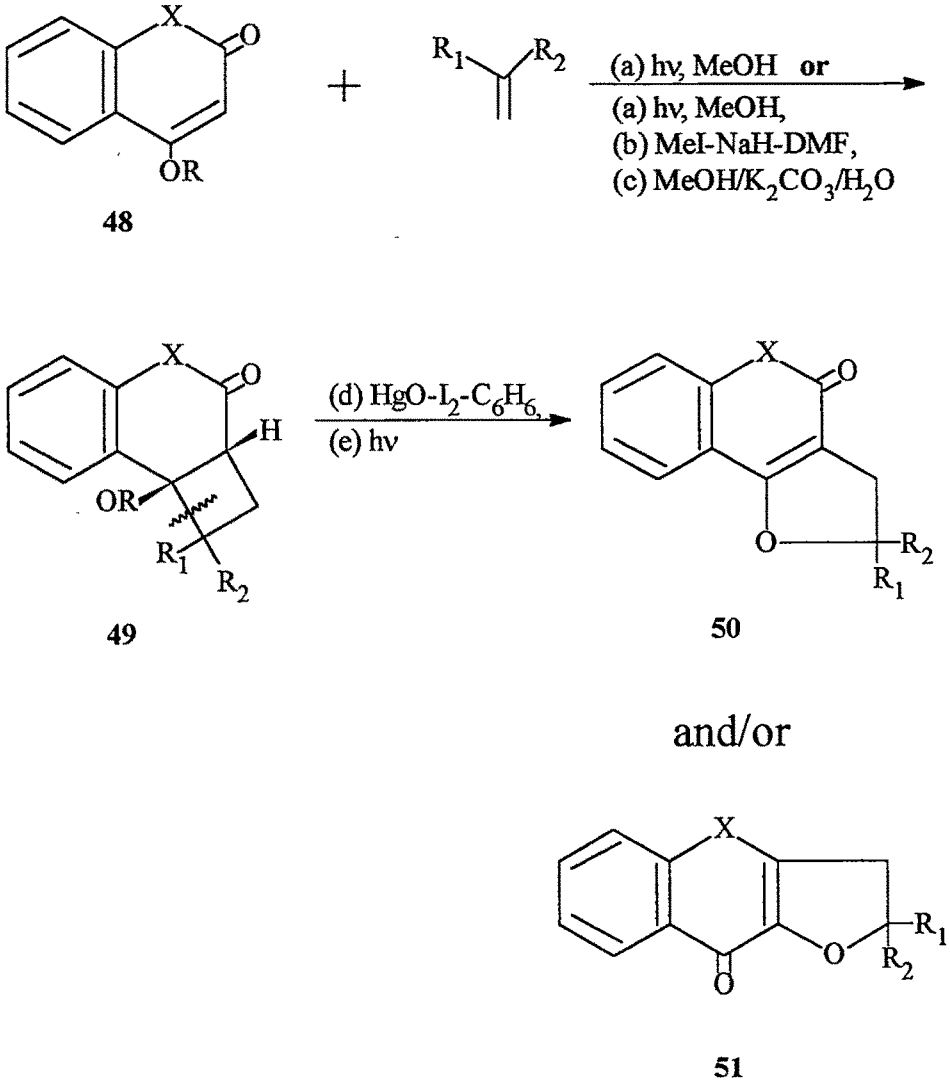
	R_1	R_2	R_3
a	H	H	CH_3
b	CH_3	H	CH_3
c	CH_3	CH_3	H



47

	R_1	R_2	R_3
a	H	H	CH_3
b	CH_3	H	CH_3
c	CH_3	CH_3	H

Scheme II.11



48

49

50

51

R = H or Ac; R_1, R_2 = alkyl, OBz, OAc, OEt, OMe

X = NMe or O

Ozonolysis and subsequent cyclization with PPA of **55** gave angelicin. **[Scheme II.13]**

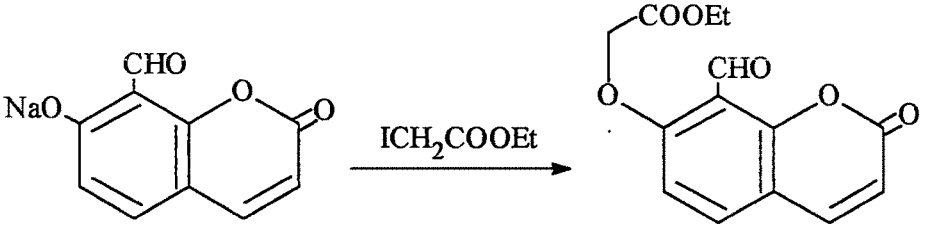
Shaikh and Trivedi[50] synthesized monofunctional psoralens 3,4-benzopsoralen **60** and 3,4-cyclohexanopsoralen **62** by condensing 2-methylresorcinol with ethylcyclohexanone-2-carboxylate to give a tricyclic coumarin **56**, which on allylation gave 7-allyloxy-8-methyl-3,4-cyclo hexanocoumarin (57). 6-Allyl isomer **58** was obtained by Claisen rearrangement followed by cyclization with conc. H_2SO_4 yielded dihydrocyclohexanocoumarin **59**. Dehydrogenation of **59** resulted in the formation of 3,4-benzopsoralen **60**. Unsubstituted furo derivative **62** was obtained by treating **58** with OsO_4 and potassium periodate to get **61** followed by cyclization with PPA. **[Scheme II.14]**

Desai and Trivedi[51] synthesized 3,4-diphenylpsoralen by carrying out the Claisen rearrangement of 7-allyloxy-8-bromo-3,4-diphenylcoumarin (63) to give o-hydroxyallyl derivative **64**, which on acetylation, bromination and subsequent cyclization gave 5′-methyl-3,4-diphenylpsoralen (65). **[Scheme II.15]**

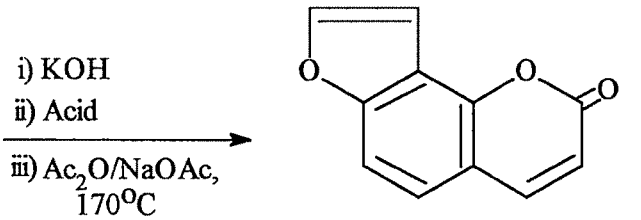
Desai and Trivedi[52] also synthesized purely monofunctional benzofurobenzopyran from 7-hydroxy-4-methylcoumarin (66) by condensing first with 2-bromocyclohexanone to give 7-(cyclohexan-2-onyloxy)-4-methylcoumarin (67). Cyclization with ethanolic KOH furnished tetrahydrobenzofurobenzopyran **68**, which on dehydrogenation produced benzofuro(3,2-g)benzopyran **69**. **[Scheme II.16]**

Chandratre and Trivedi[53] prepared monofunctional psoralen, 2-oxo-2H-benzofuro(3,2-g)benzopyran (75) by a different route by condensing 2-bromocyclohexanone with resacetophenone to yield **70**, which on cyclization with alkali gave benzofuran **71**. Pyrone ring was built up by condensing it with diethylcarbonate in the presence of pulverized sodium afforded 4-hydroxy-6,7,8,9-tetrahydrobenzofuro(3,2-g)benzopyran-2H-one (72). Tosylation of hydroxy group afforded **73** followed by reductive detosyloxylation with zinc

Scheme II.12

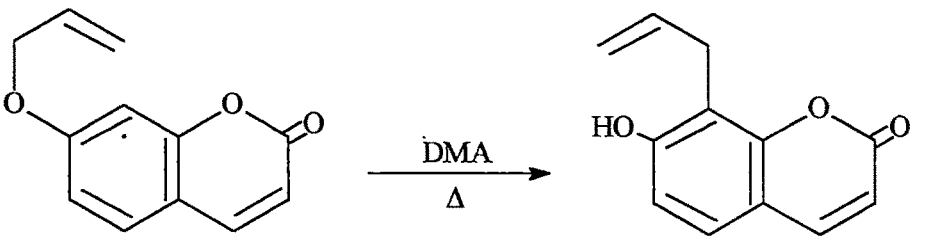


52 53

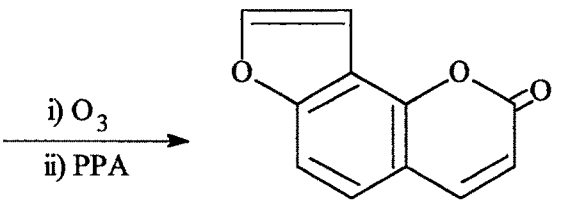


7

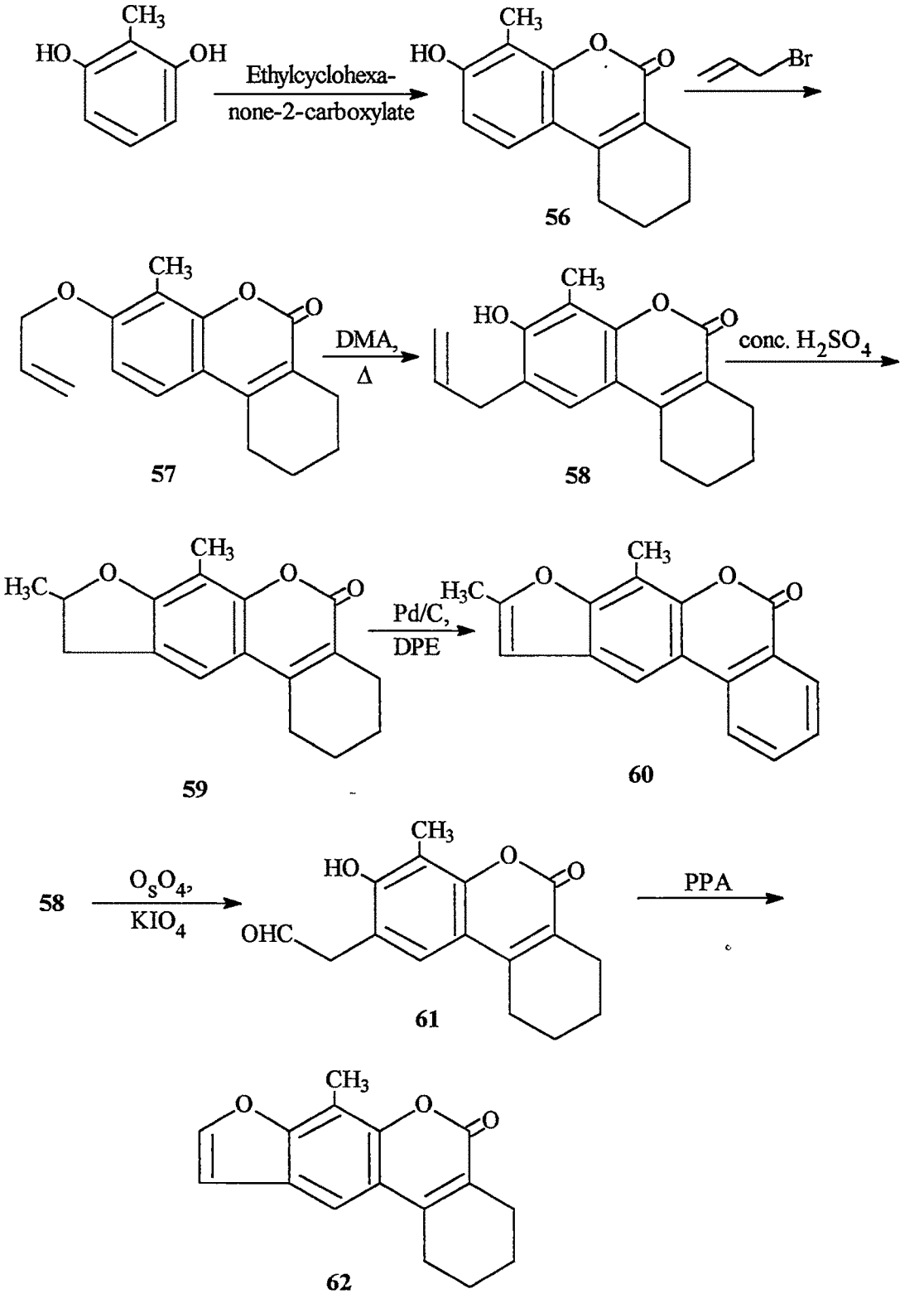
Scheme II.13



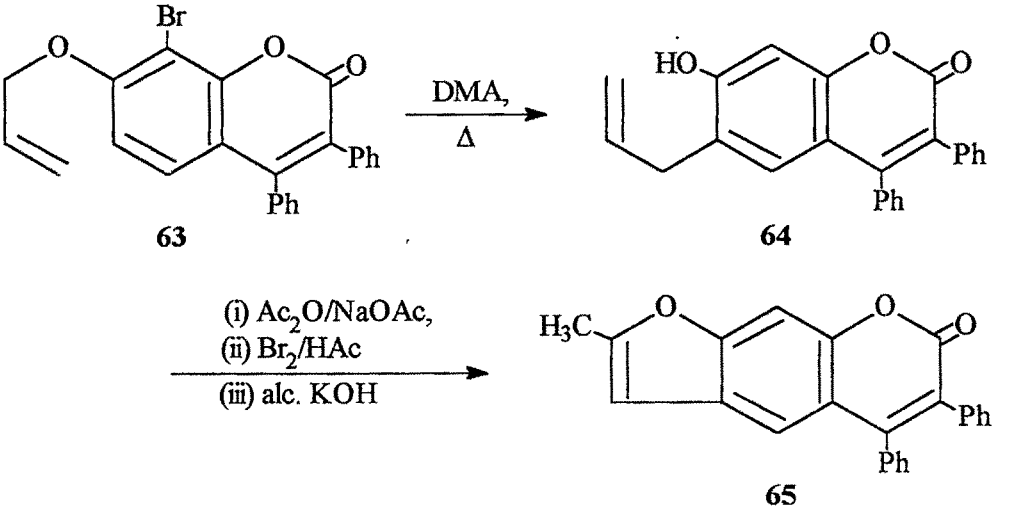
54 55



Scheme II.14

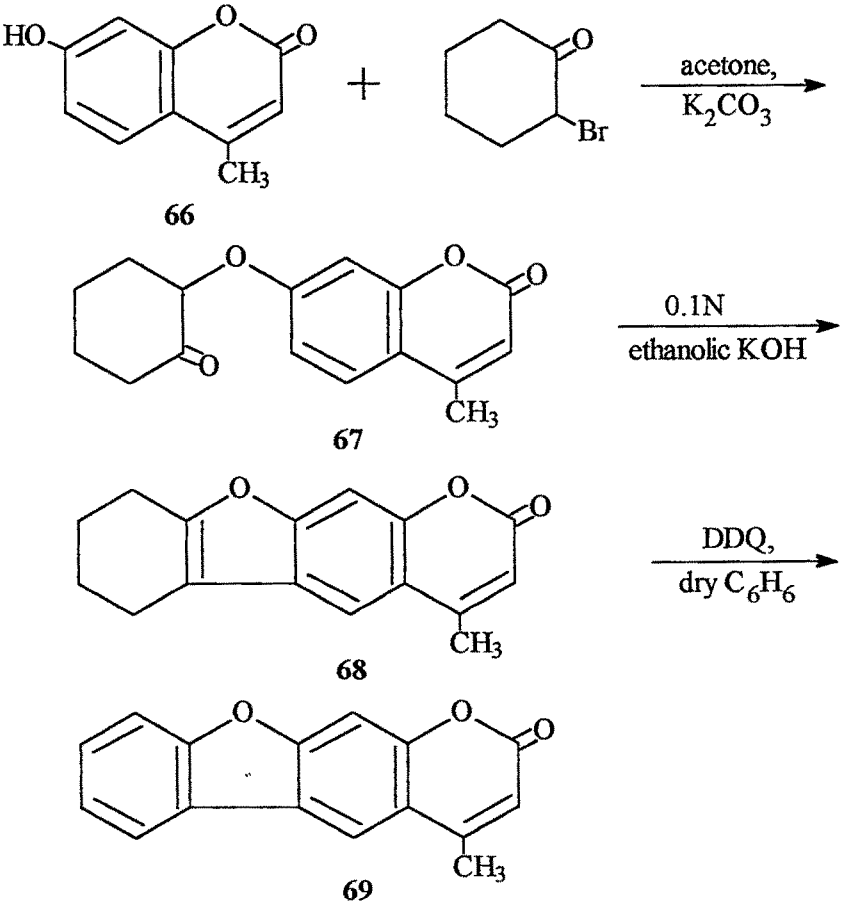

CH3
HO
OH
Ethylcyclohexa-
none-2-carboxylate
HO
O
O
Br
56
CH3
O
O
O
DMA,
Δ
57
CH3
HO
O
O
conc. H2SO4
58
H3C
O
CH3
O
O
Pd/C,
DPE
59
60
58
OsO4,
KIO4
HO
OHC
PPA
61
62

Scheme II.15



63 64 65

Scheme II.16



66 67 68 69

and HCl gave 6,7,8,9-tetrahydro-2-oxo-2H-benzofuro(3,2-g)benzopyran (74), which on dehydrogenation produced benzofurobenzopyrone **75**. **[Scheme II.17]**

Adam *et al.*[54] reported a synthesis of novel furonaphthopyrone in good yield with a benzene spacer to serve as potential monofunctional, photobinding agent. 1,5-Naphthalenediol (76) was first converted into naphthopyrone **77** by Pechmann condensation, which on condensation with 3-chloro-2-butanone gave ether **78**. The cyclization was carried out with $POCl_3$ to obtain furonaphthopyrone **79**. **[Scheme II.18]**

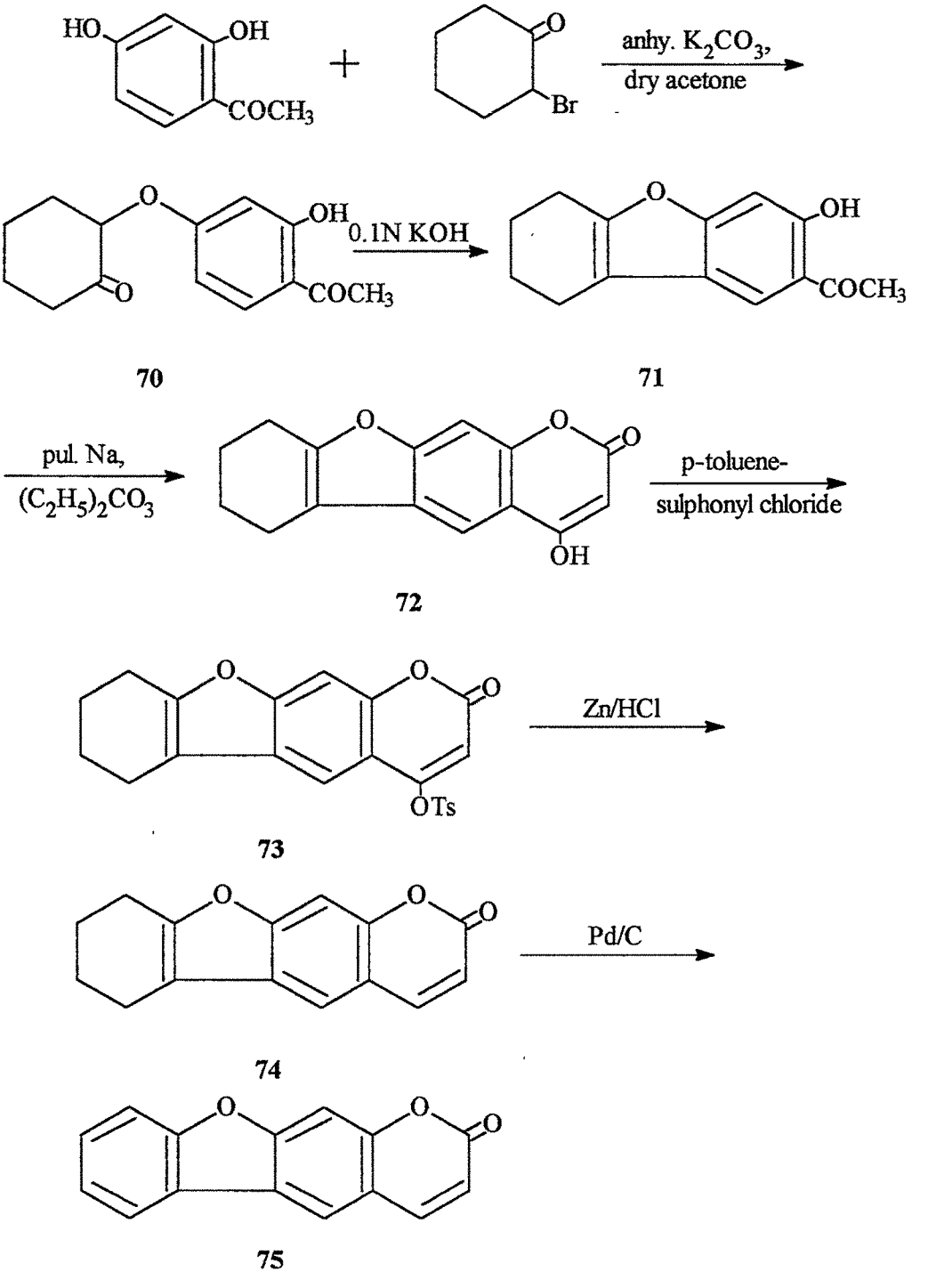
The same method for making monofunctional compounds by keeping benzene spacer was further extended by Zhi-Fu Tao *et al.*[8] to synthesize furonaphthopyrones **84**. 2,7-Naphthalenediol (80) on Pechmann condensation yielded naphthopyrones **81** and **82**. **81** was reacted with 2,3-dibromopropene to give ether **83** followed by Claisen rearrangement gave **84**. **[Scheme II.19]**

Hismat *et al.*[55] synthesized substituted psoralen by Friedel-Crafts acylation of 2,3-dipenyl-6-methoxybenzofuran (85) with phenylacetylchloride produced a mixture of two products; mono- and di- phenylacetyl derivatives **86**, **87**. After the separation, **87** was treated with diethylcarbonate in presence of powdered sodium metal to yield 2,3,6-triphenyl-5-hydroxy-9-phenylacetyl-7H-furo(3,2-g)[1]benzopyran-7-one (88). **[Scheme II.20]**

Queval and Bisagni[56] synthesized more effective nontoxic and noncarcinogenic monofunctional psoralen, reported to exhibit the therapeutic activity as 8-MOP without any local hyperpigmentation from methoxy coumarilate **89**, which on formylation afforded 5-formyl-6-methoxycoumarilate (90). Hydrolysis of **90** followed by decarboxylation and demethylation yielded benzofuran **91**, which on condensation with diethylmalonate produced 3-carboethoxypsoralen (12). **[Scheme II.21]**

Sinha *et al.*[57] made a novel type of furocoumarin which also exhibits good antifertility activity. 6,7-Dihydro-4,13-dimethylbis-1-benzopyrano

Scheme II.17



70 **71**

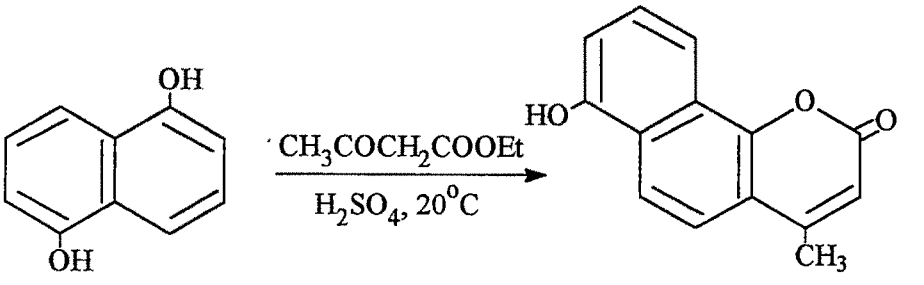
72

73

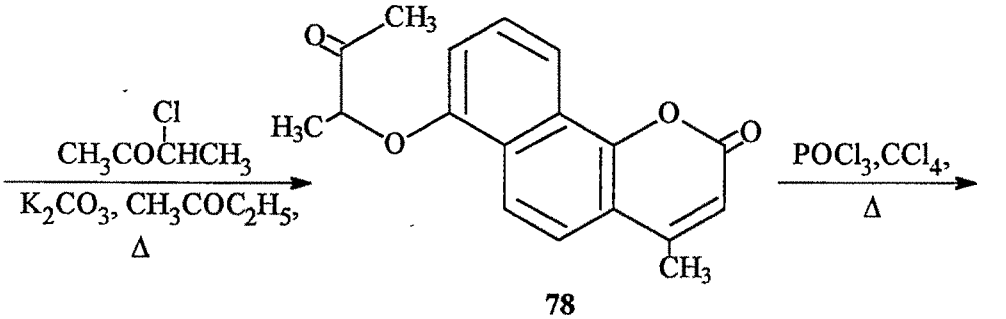
74

75

Scheme II.18



76 **77**



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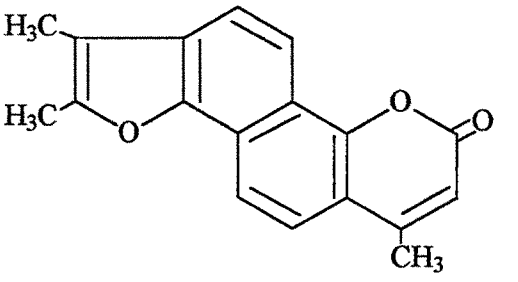
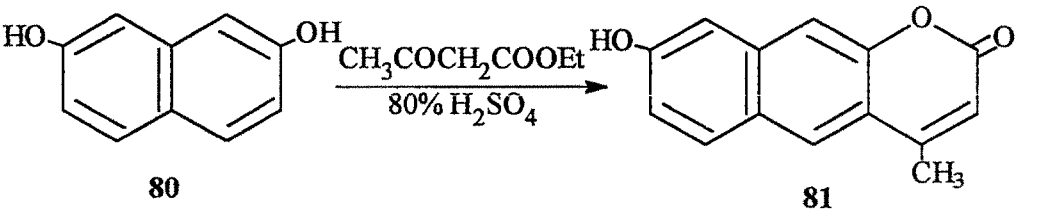


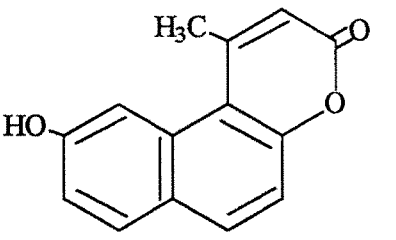
79

Scheme II.19

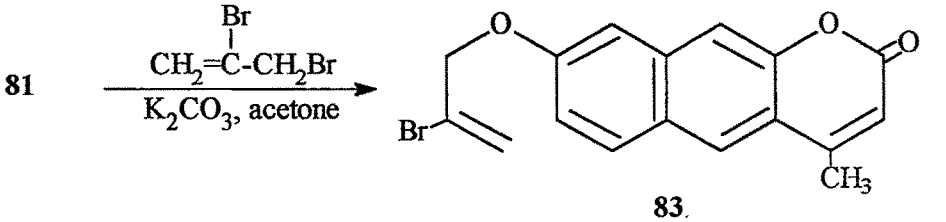


80 **81**

+



82



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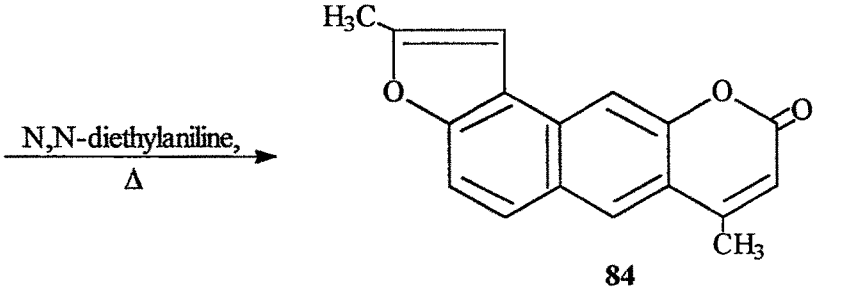
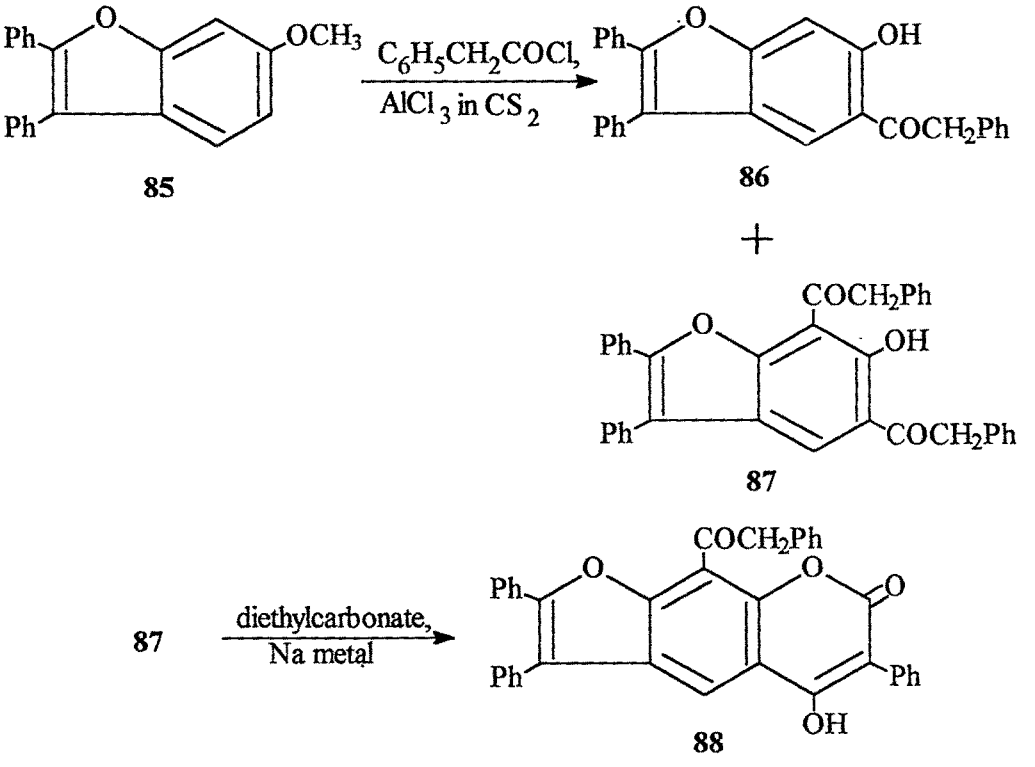
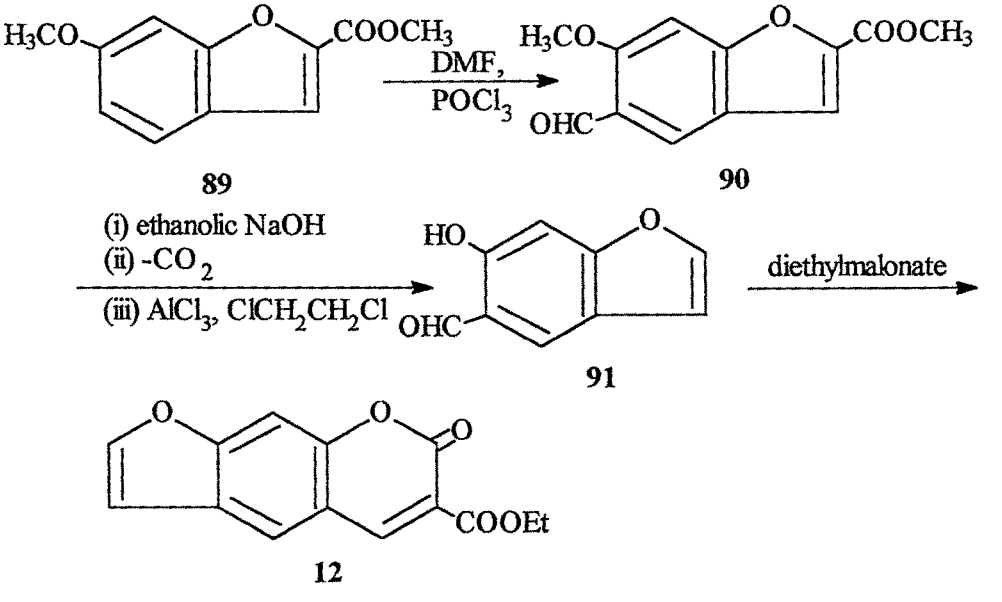


84

Scheme II.20



Scheme II.21

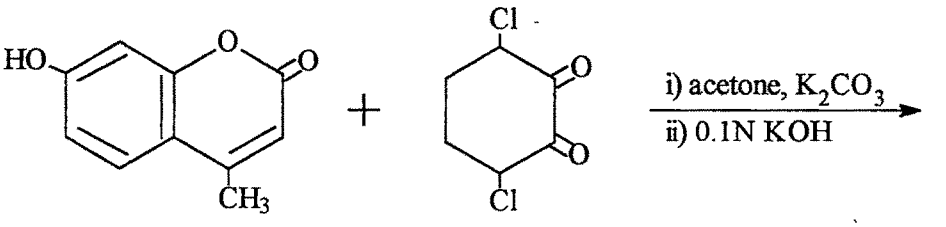


[6,7-d:7′,6′-d′]-2H,11H-benzo[1,2-b:3,4-b′]difuran-2-one (92) was prepared by the condensation of 7-hydroxy-4-methylcoumarin (66) and 3,6-dichloro cyclohexane-1,2-dione followed by cyclization. **[Scheme II.22]**

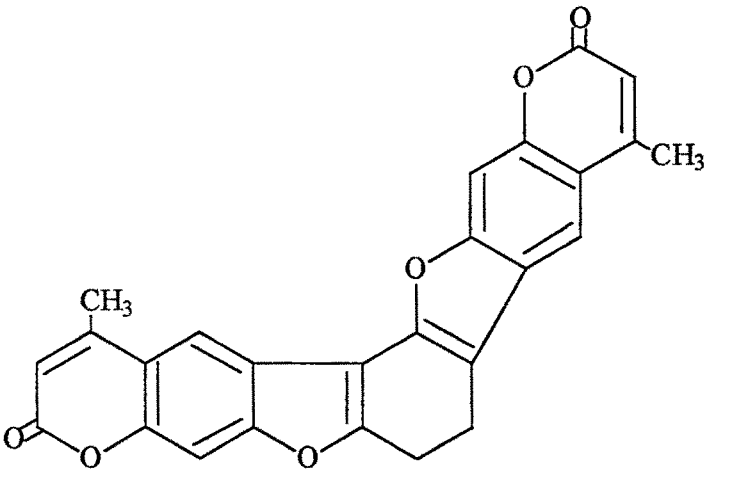
Traven *et al.*[58] developed a new method for angelicin via transformations of 7-hydroxy-8-halogenoacetyl-4-methylcoumarin in satisfactory yields. 7-Acetoxy-4-methylcoumarin (93) was first subjected to Fries rearrangement to yield 8-acetyl-7-hydroxy-4-methylcoumarin[59] (94), which on bromination with 2 moles of bromine yielded 3-bromo-8-bromoacetyl-7-hydroxy-4-methyl coumarin (95). Reduction of **95** with $NaBH_4$ gave 3-bromo-8-(2′-bromo-1′-hydroxyethyl)-7-hydroxy-4-methylcoumarin (96), which on reaction with K_2CO_3 in DMSO produced 3-bromo-9-hydroxy-4-methyldihydrofuro[2,3-h] coumarin (98). **98** was then subjected to dehydration with H_2SO_4 to yield 3-bromo-4-methylangelicin (99). Final product 7-methylangelicin (100) was achieved by treating **99** with zinc dust in alcohol. **[Scheme II.23]**

Zoubir *et al.*[60] synthesized monofunctional psoralen analogues dihydrothienofurocoumarins **104a-c** having a fused dihydrothiophene ring on the 3,4 site. They also studied the absorbance and fluorescence spectra to perform the photochemical and photobiological experiments. They achieved it by condensing 3-methoxyphenol with 3-chlorobutan-2-one followed by cyclization with $POCl_3$ gave benzofuran derivative **101**, which was demethylated, acetylated followed by Fries migration to yield **102**. Condensation of **102** with aldehyde afforded **103a-c**. Desired product **104a-c** was obtained by condensing it with ethylthioglycolate using Xicluna and Ombetta's procedure[61,62]. **[Scheme II.24]**

Scheme II.22

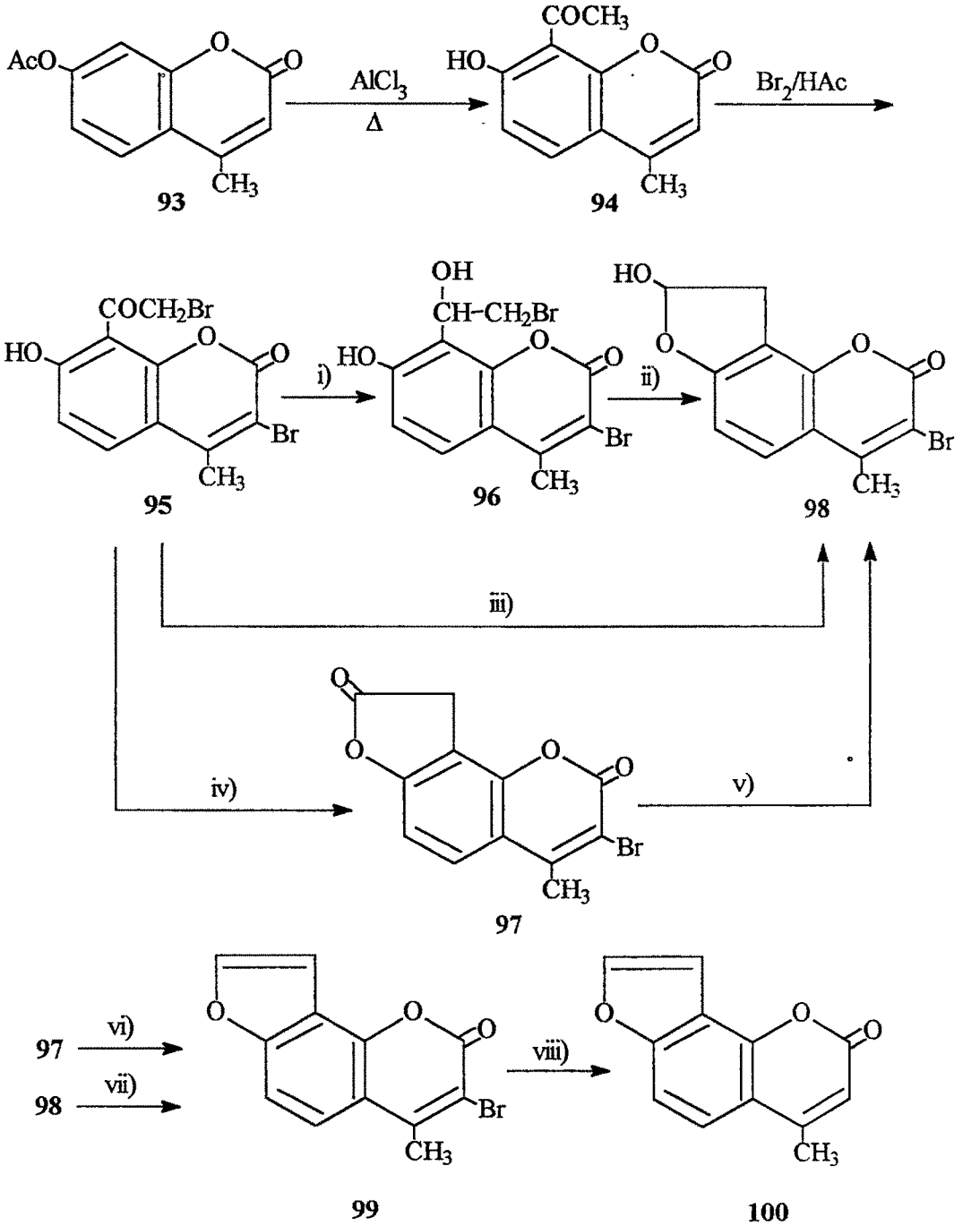


66



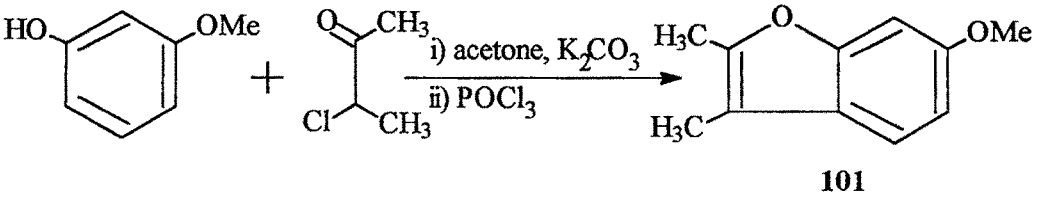
92

Scheme II.23



i) $NaBH_4$, dioxane; ii) K_2CO_3, DMSO; iii) (1) $NABH_4$, dioxane, (2) K_2CO_3; iv) K_2CO_3, DMSO; v) $NaBH_4$, dioxane; vi) $NaBH_4$, dioxane; vii) 74% H_2SO_4; viii) Zn, ethanol

Scheme II.24



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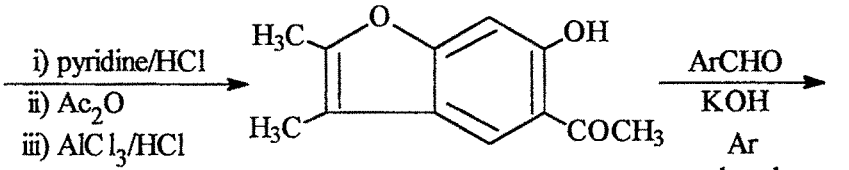
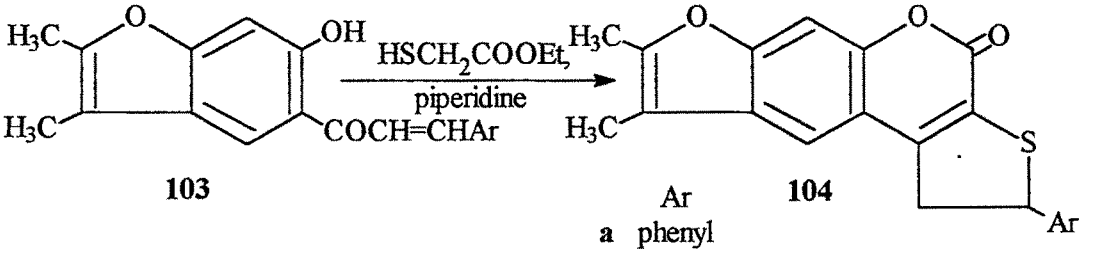


102

Ar
a phenyl
b furyl
c p-anisyl



103

104

Ar
a phenyl
b furyl
c p-anisyl

PRESENT WORK

The present work of this chapter incorporates the study and syntheses of furobenzopyrones having an electron withdrawing group such as $-COOC_2H_5$, $-COCH_3$ and -CN at position 3 on the pyrone ring system as these are reported to produce[63,64] only monoadducts which will cause minimum side effects in PUV-A therapy. These compounds are although synthesized by earlier workers e. g. Bisagni *et al.*[56] involve multiple steps and overall poor yields, therefore we planned an alternative method using Claisen rearrangement as the key step. In this method different 7-allyloxy benzopyrones containing electron withdrawing group have been subjected to Claisen rearrangement followed by cyclization and dehydrogenation to synthesize both angular as well as linear counterparts to study the chemistry and synthetic aspects of these compounds.

Claisen rearrangements of the following allyloxy derivatives were studied.

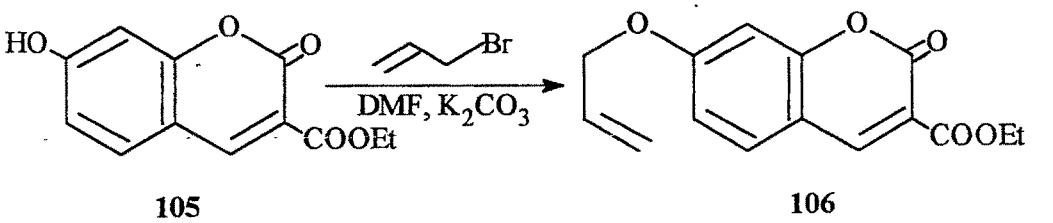
- ethyl-7-allyloxybenzopyran-2H-one-3-carboxylate
- ethyl-7-allyloxy-8-iodobenzopyran-2H-one-3-carboxylate
- 7-allyloxy-3-acetylbenzopyran-2H-one
- 7-allyloxy-8-iodo-3-acetylbenzopyran-2H-one
- ethyl-7-allyloxy-8-methylbenzopyran-2H-one-3-carboxylate
- 7-allyloxy-3-cyanobenzopyran-2H-one
- ethyl-2,4-diallyloxy-α-cyanocinnamate
- ethyl-2,4-diallyloxy-α-carboethoxycinnamate
- E ,Z-ethyl-2,4-diallyloxy-α-acetylcinnamate

Synthesis of ethyl-2-methylfuro(2,3-h)benzopyran-5H-one-6-carboxylate (109) was carried out from ethyl-7-hydroxybenzopyran-2H-one-3-carboxylate (105), which was prepared by Knoevenagel method, on allylation with allylbromide in the presence of anhydrous potassium carbonate in dry N,N-dimethylformamide gave ethyl-7-allyloxybenzopyran-2H-one-3-carboxylate (106) in 80% yield. Very poor yield was observed when dry

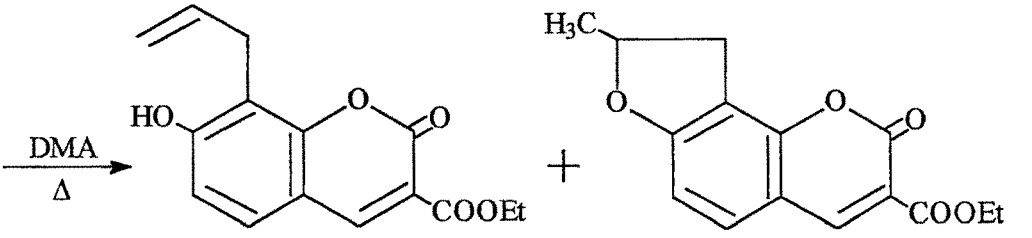
acetone was used in place of DMF as a medium for allylation. **[Scheme II.25]** The structure of **106** was confirmed by its elemental analysis, IR spectrum which showed absorption band in KBr at 1761cm^{-1} for >CO of lactone and >CO of ester **[Fig. II.1]** while PMR spectrum exhibited signals in $CDCl_3$ at δ 1.45, a triplet for three methyl protons of ester at C-3; a quartet at 4.40 for two methylene protons of ester at C-3; a doublet at 4.65 for two protons in allyloxy chain -OC$\underline{H_2}$CH=CH$_2$ at C-7; two multiplets obtained at 5.25-5.60 and 5.85-6.30 for three protons of -OCH$_2$CH=C$\underline{H_2}$ and -OCH$_2$C$\underline{H}$=CH$_2$ at C-7 respectively; another multiplet at 6.75-7.00 for two ortho coupled protons at C-6 and C-8; again one doublet at 7.55 for one proton of C-5 and a singlet for one proton of C-4 at 8.45. **[Fig. II.2]**

106 on Claisen rearrangement in refluxing N,N-dimethylaniline for 7.5h produced a mixture of two isomers as alkali soluble and alkali insoluble. Alkali soluble product was separated by stirring the crude reaction mixture with mild alkali for 15 minutes. The structure of **107** was assigned from the elemental analysis, IR spectrum which showed absorption bands in KBr at 3272, 1750 and 1710cm^{-1} for hydroxyl group and two >CO groups **[Fig. II.3]** and PMR spectrum as ethyl-7-hydroxy-8-allybenzopyran-2H-one-3-carboxylate, which exhibited signals in $CDCl_3$ and DMSO as δ 1.40, a triplet for three methyl protons of ester at C-3; a doublet at 3.55 for two methylene protons of -C$\underline{H_2}$-CH=CH$_2$ at C-8; a quartet at 4.30 for two methylene protons of ester at C-3; two multiplets appeared at 4.80-5.20 and 5.60-6.10 for two methylene protons of -CH$_2$-CH=C$\underline{H_2}$ and for a proton of -CH$_2$-C$\underline{H}$=CH$_2$ at C-8 respectively. Two doublets at 6.85, J = 9Hz and 7.25, J = 9Hz for proton at C-6 and C-5 and a singlet at 8.30 for a proton at C-4. **[Fig. II.4]** The alkali insoluble product was purified and its structure was established from elemental analysis, IR spectrum which showed absorption bands in KBr at 1756cm^{-1} for two >CO groups **[Fig. II.5]** and PMR spectrum as ethyl-2-methyl-2,3-

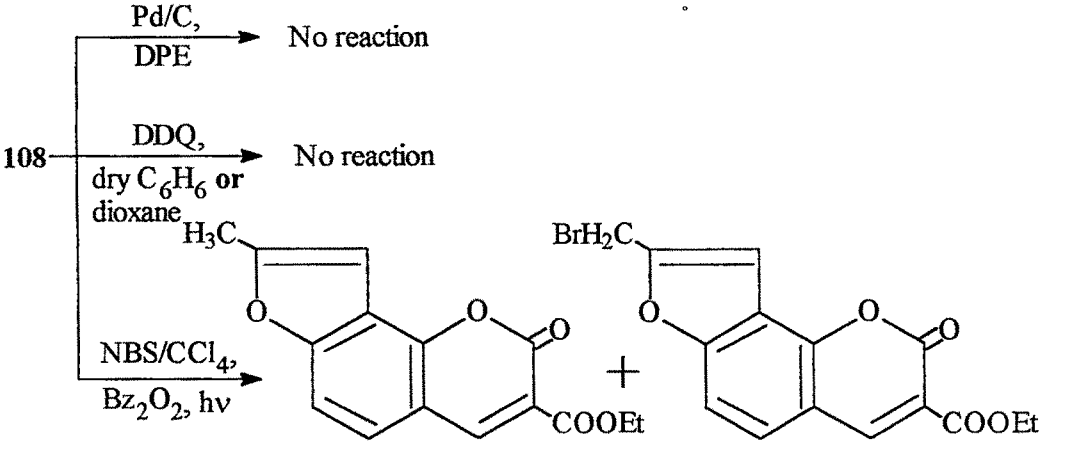
Scheme II.25



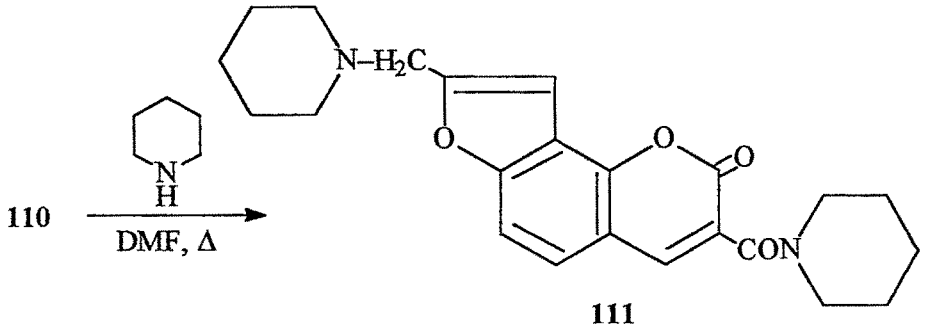
105 106



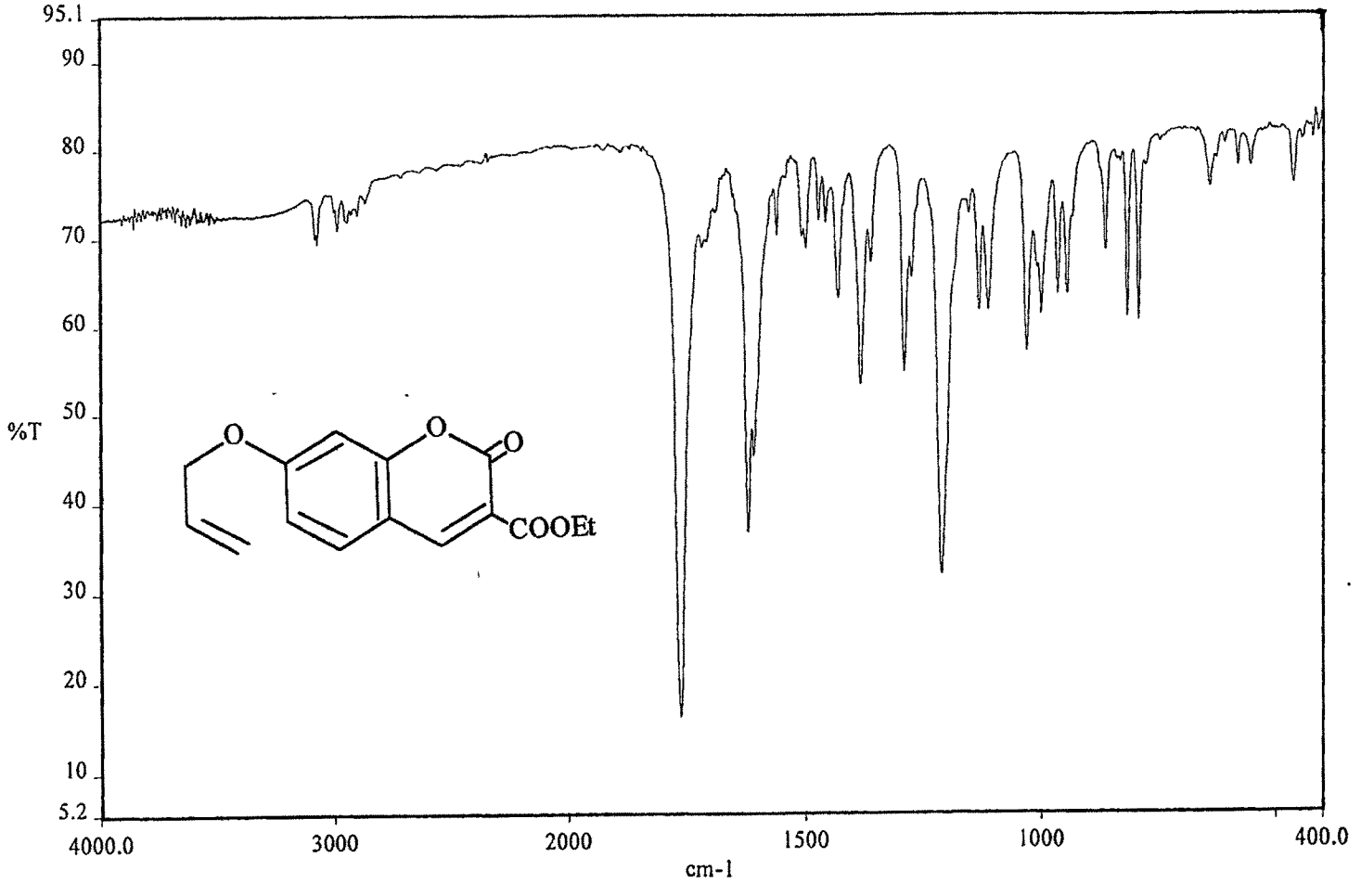
107 108



109 110



111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90
80
70
60
50
40
30
20
10
5.2
%T
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3000
2000
1500
1000
400.0
cm-1
O
O
O
COOEt

Fig. II.1

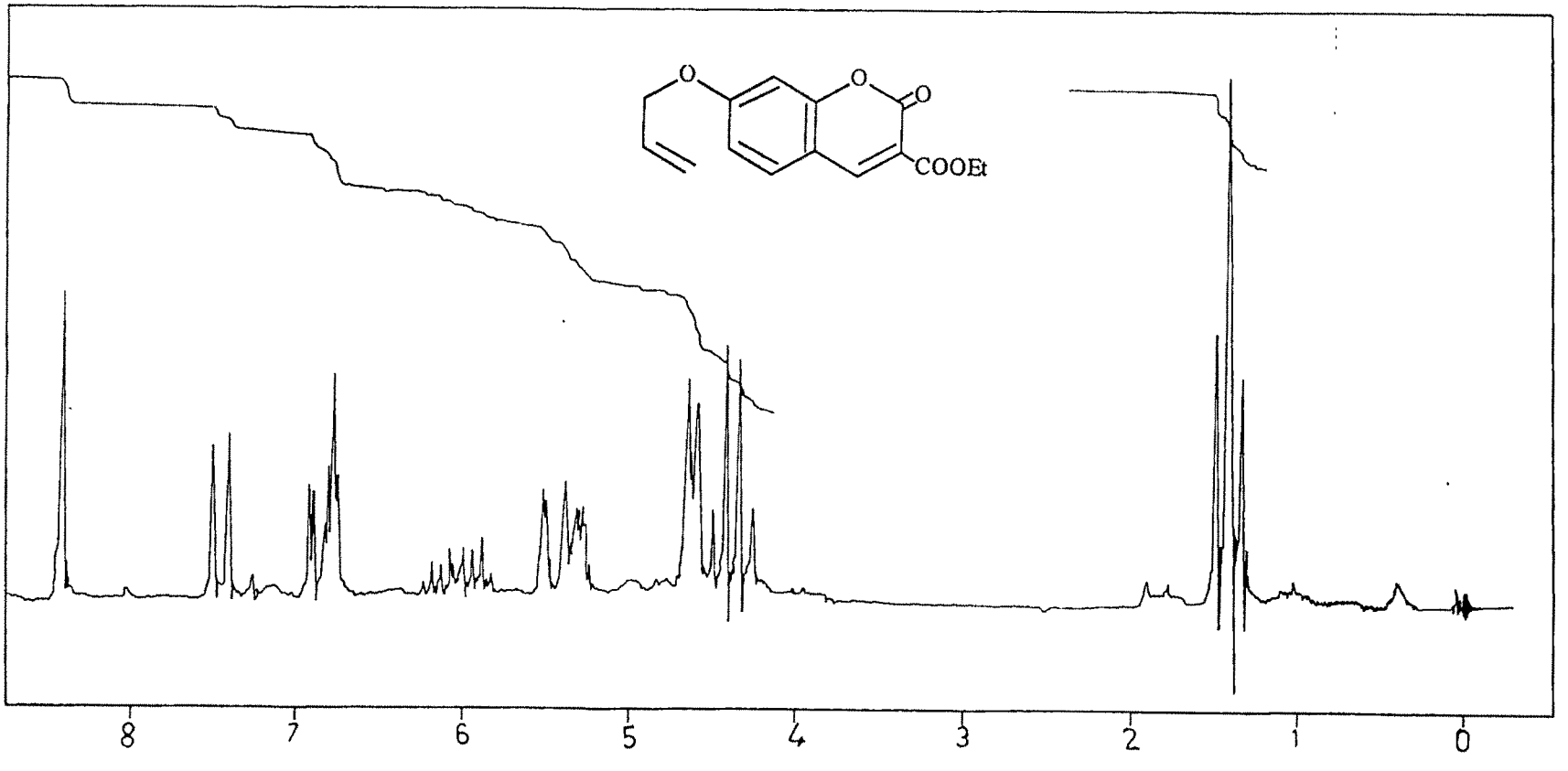


Fig. II.2

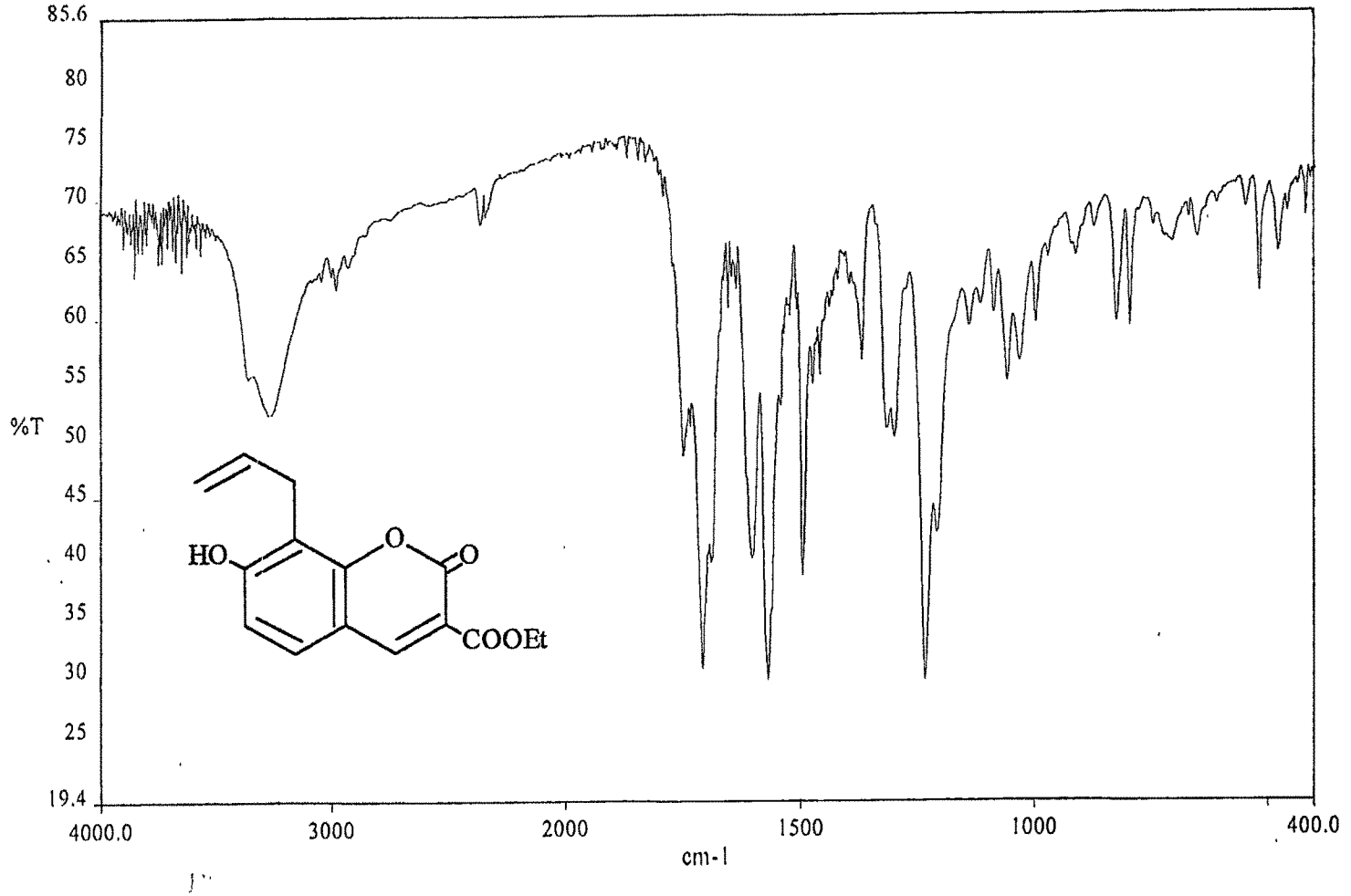

85.6
80
75
70
65
60
55
%T
50
45
40
35
30
25
19.4
4000.0
3000
2000
1500
1000
400.0
cm-1
HO
O
O
COOEt

Fig. II.3

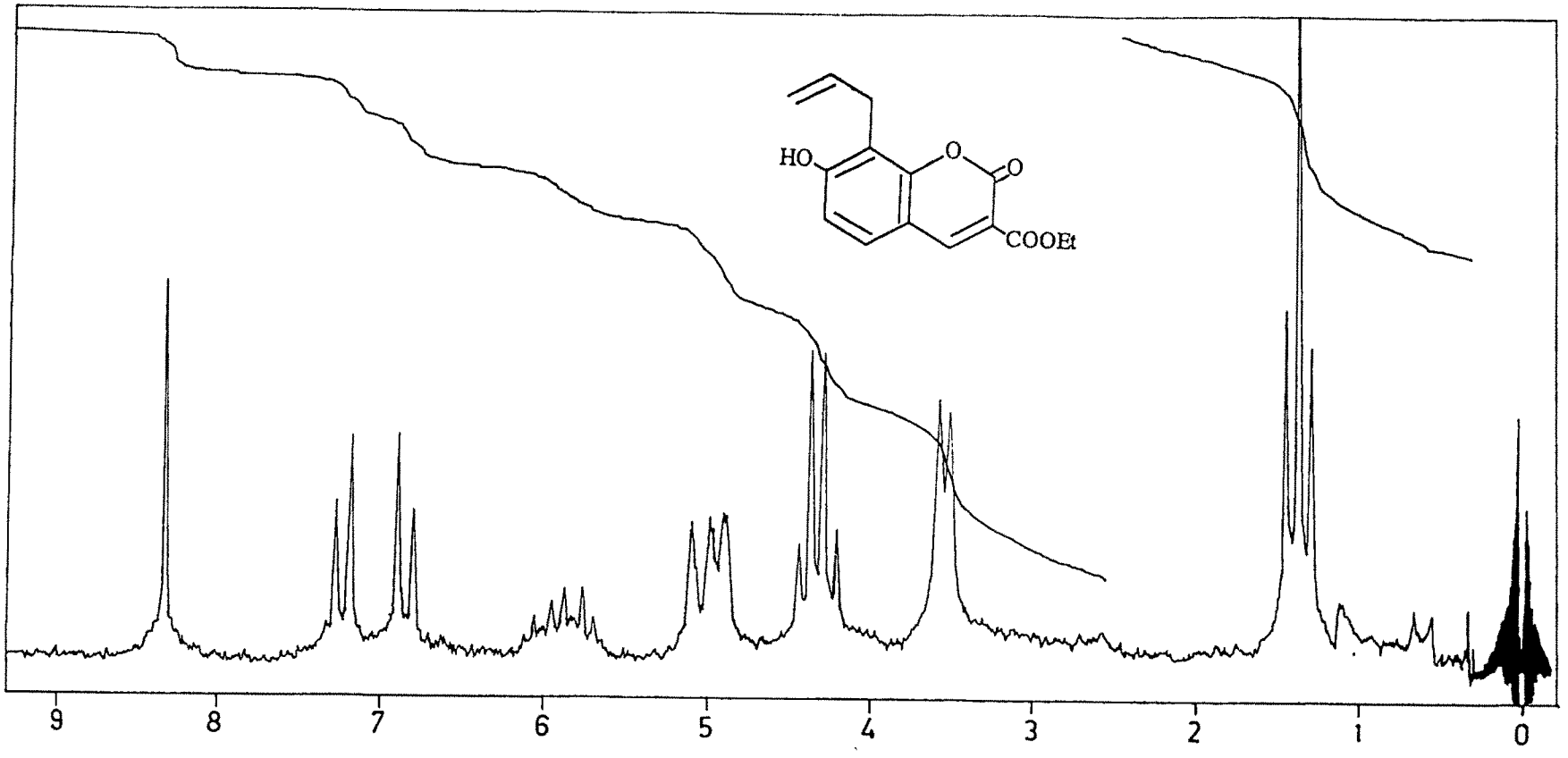


Fig. II.4

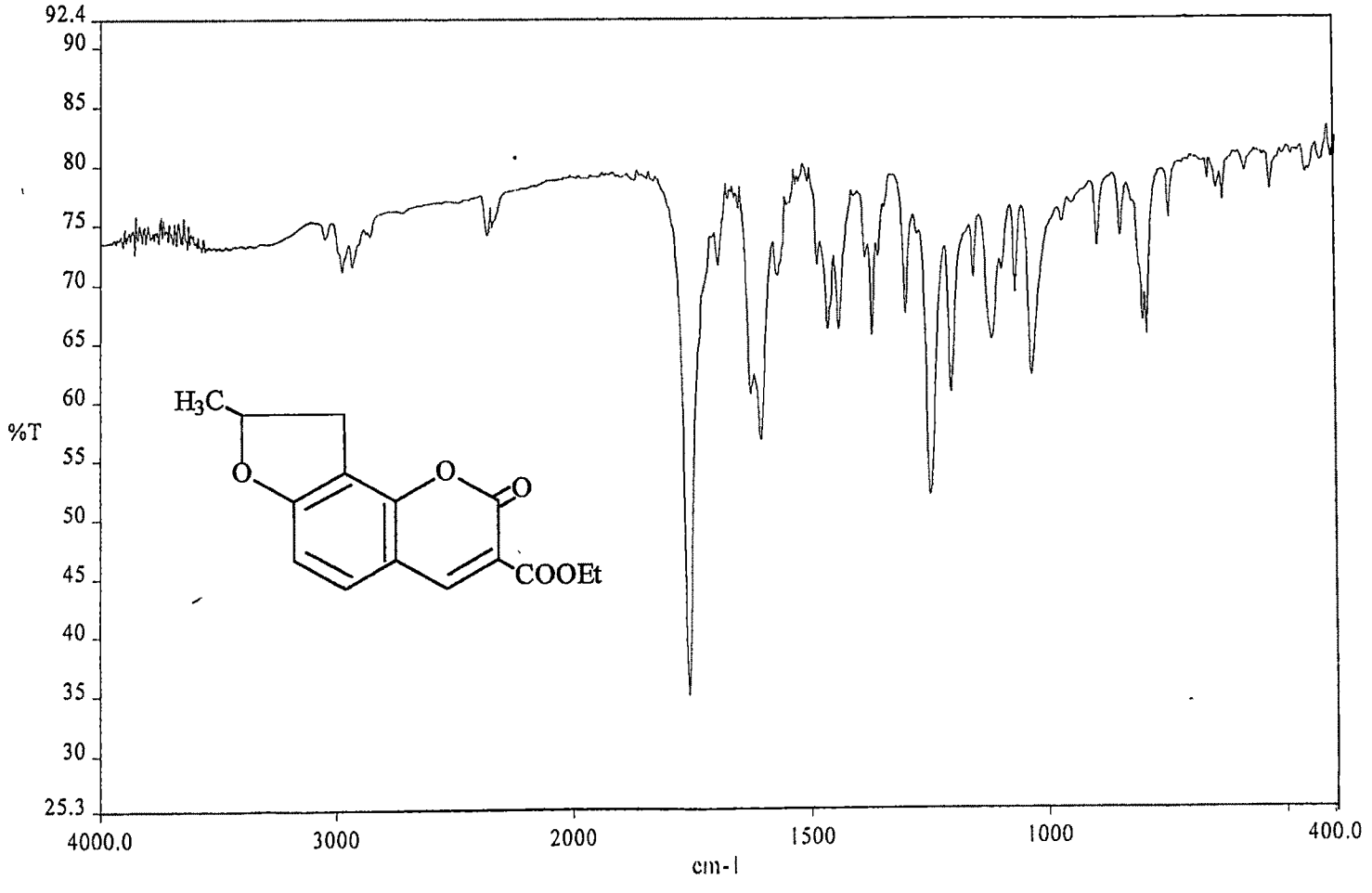

92.4
90
85
80
75
70
65
60
55
50
45
40
35
30
25.3
%T
4000.0
3000
2000
1500
1000
400.0
cm-1
H3C
O
O
O
O
COOEt

Fig. II.5

dihydrofuro(2,3-h)benzopyran-5H-one-6-carboxylate (108). It exhibited signals in $CDCl_3$ at δ 1.40, a triplet for three methyl group protons of ester at C-6; a doublet at 1.55 for three methyl group protons at C-2; a multiplet at 2.80-3.65 for two protons at C-3; a quartet at 4.45 for three methylene protons of ester at C-6; another multiplet at 5.00-5.30 for a proton at C-2; two doublets at 6.75, J = 9Hz and 7.40, J = 9Hz for protons at C-9 and C-8 and a singlet appeared at 8.45 for a proton at C-7. **[Fig. II.6]**

The above Claisen rearrangement was also studied varying the refluxing time of the reaction. When the reaction was carried out for 5h, it also left some unreacted starting allyloxy compound along with **107** and **108**. Similarly when refluxed for 10h, it produced only **108**. It was also observed that ethyl-7-hydroxy-8-allylbenzopyran-2H-one-3-carboxylate (107), one of the Claisen rearrangement product when heated in refluxing DMA for 6h gave only the dihydrofuro product **108**. In all the above cases the formation of products were confirmed by monitoring with TLC and from their melting points.

The above observations indicate that during Claisen rearrangement, the allyl group first undergoes migration to the 8^{th} position to form 7-hydroxy-8-allyl product, which subsequently cyclizes to give 2,3-dihydrofuro isomer as an alkali insoluble product **108**.

108 was then subjected to dehydrogenation with Pd/C (10%) in refluxing diphenylether for 6h to 24h and DDQ in dry benzene or dioxane for 24h failed to give desired ethyl-2-methylfuro(2,3-h)benzopyran-5H-one-6-carboxylate (109). In all the attempts only starting compound **108** was recovered.

As the above methods failed to give angular furocoumarin, it was envisaged to use NBS to generate the double bond at 2,3- position in the dihydrofuran ring system to get the desired furobenzopyrone[65,66].

Dehydrogenation of ethyl-2-methyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one-6-carboxylate (108) was carried out with N-bromosuccinimide in the presence of benzoylperoxide using CCl_4 as solvent under 200W-tungsten lamp, which resulted in the formation of a mixture of two products. These products

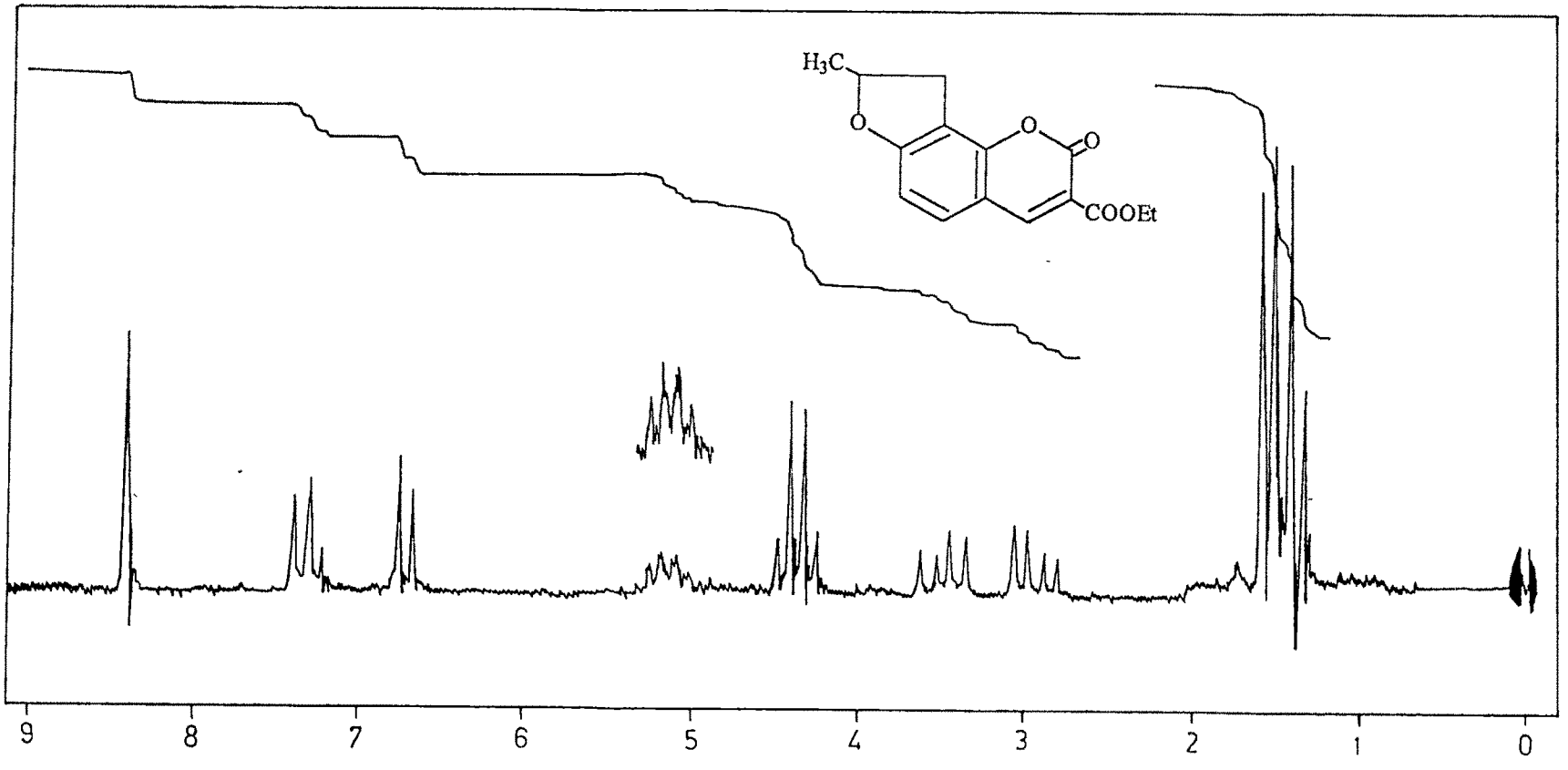


Fig. II.6

were separated by fractional crystallization. The structures of the products were established from their elemental analysis, IR and PMR spectra as ethyl-2-methylfuro(2,3-h)benzopyran-5H-one-6-carboxylate (109) and ethyl-2-bromomethylfuro(2,3-h)benzopyran-5H-one-6-carboxylate (110). **109** exhibited bands in IR spectrum at 1756, 1699cm^{-1} for >CO of lactone and ester respectively **[Fig. II.7]** and its PMR signals in $CDCl_3$ at δ 1.40, a triplet for three methyl group protons of ester at C-6; a singlet at 2.50 for three methyl group protons at C-2; a quartet appeared at 4.40 for two methylene protons of ester at C-6; a singlet at 6.70 for proton at C-3; a multiplet appeared for ortho coupled protons at C-9 and C-8 at 7.30 and a singlet for proton C-7 at 8.45. **[Fig. II.8]** **110** showed bands in IR at 1740, 1699cm^{-1} for >CO of lactone and ester **[Fig. II.9]** and its PMR signals in $CDCl_3$+DMSO at δ 1.42, a triplet for three methyl group protons of ester at C-6; a quartet at 4.45 for two methylene protons of ester at C-6; at 4.60 singlet obtained for two methylene protons of -C$\underline{H_2}$Br at C-2, another singlet at 7.10 for proton at C-3; two doublets at 7.46, J = 9Hz and 7.55, J = 9Hz for two ortho coupled protons at C-9 and C-8 respectively and at 8.60 singlet appeared for C-7 proton. **[Fig. II.10]**

The downfield shift of signal at δ 2.50 in **109** to 4.60 in **110** indicates the substitution of bromine on methyl group at position C-2. The formation of **110** was further confirmed by condensing it with a secondary amine piperidine, which gave 2-piperidinomethyl-6-piperidinocarbonylfuro(2,3-h)benzopyran-5H-one (111). It showed signals in $CDCl_3$ at δ 1.45-1.65; a multiplet for twelve protons of six methylene groups at C-3′, C-4′, C-5′ and C-3″, C-4″, C-5″; a multiplet at 2.50 for four protons of two methylene groups at C-2′ and C-6′; a singlet at 3.35 for two methylene protons at C-2; at 3.70, a broad signal for four protons of two methylene groups at C-2″ and C-6″; another singlet at 6.85 for C-3 proton; two ortho coupled protons appeared as doublet at 7.35, J = 7.5Hz and 7.45, J = 7.5Hz for C-9 and C-8 respectively; and a singlet for proton C-7

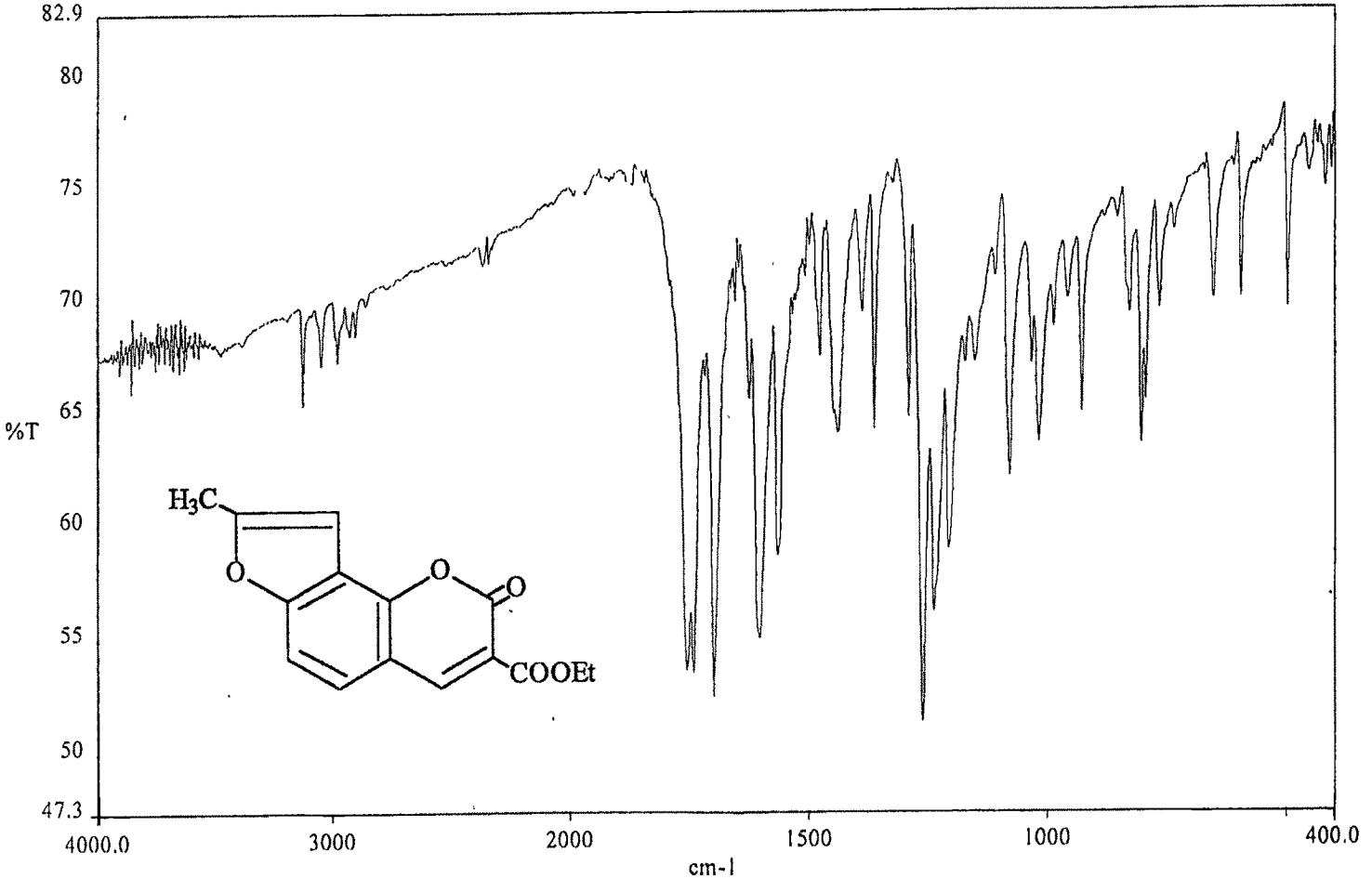

82.9
80
75
70
65
60
55
50
47.3
%T
4000.0
3000
2000
1500
1000
400.0
cm-1
H3C
O
O
O
COOEt

Fig. II.7

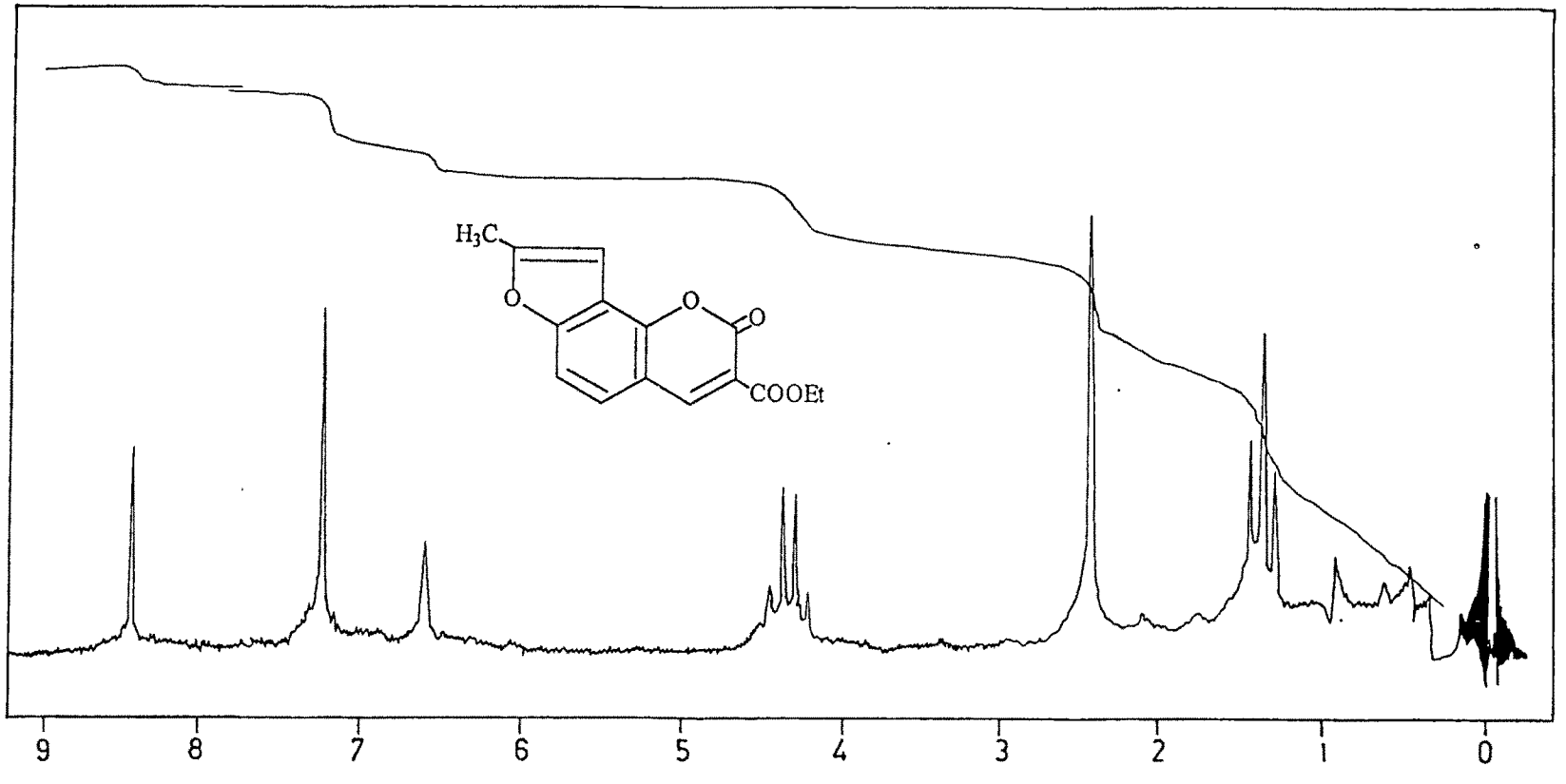
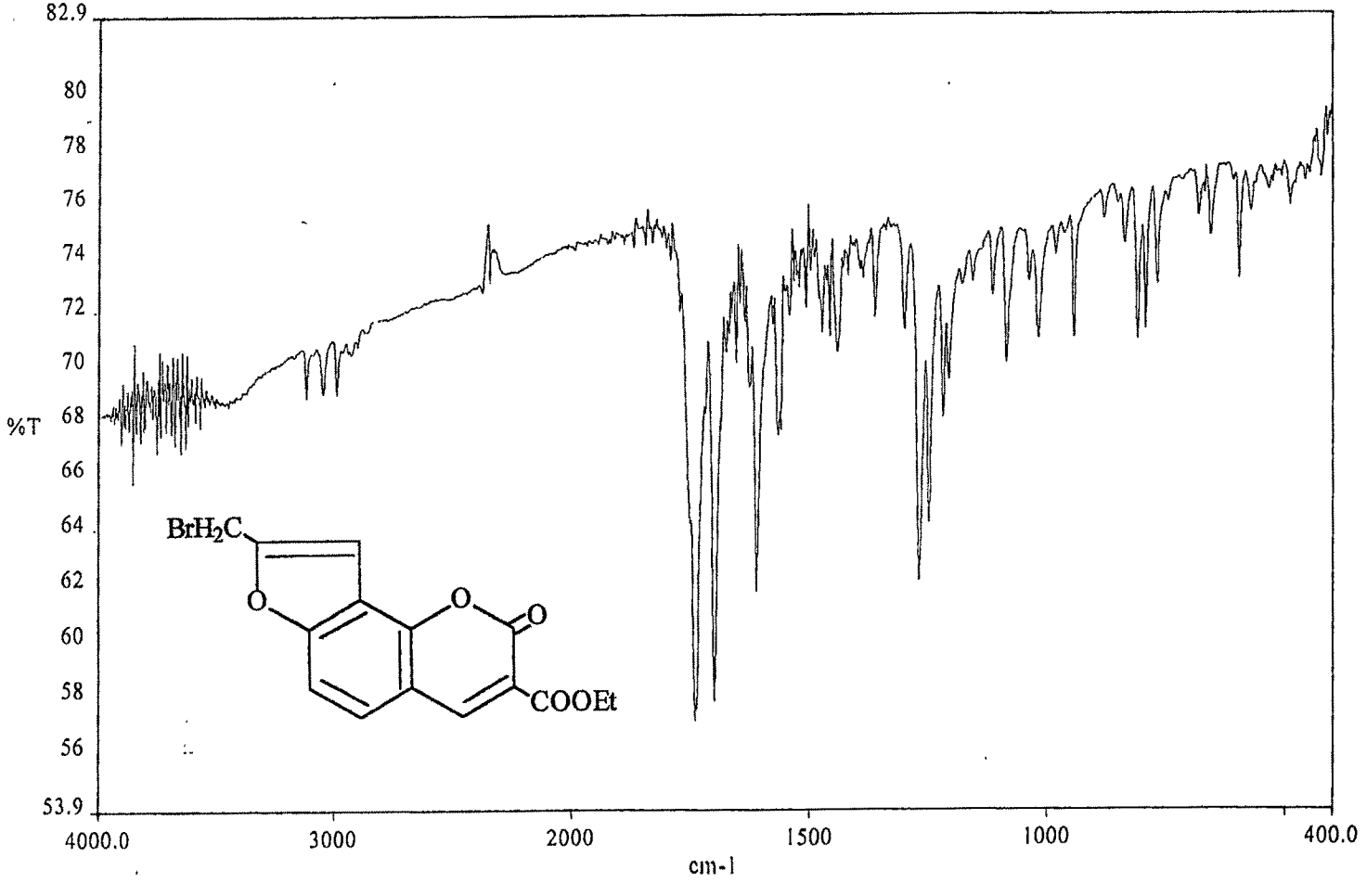


Fig. II.8


82.9
80
78
76
74
72
70
68
66
64
62
60
58
56
53.9
%T
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3000
2000
1500
1000
400.0
cm-1
BrH2C
O
O
O
COOEt

Fig. II.9

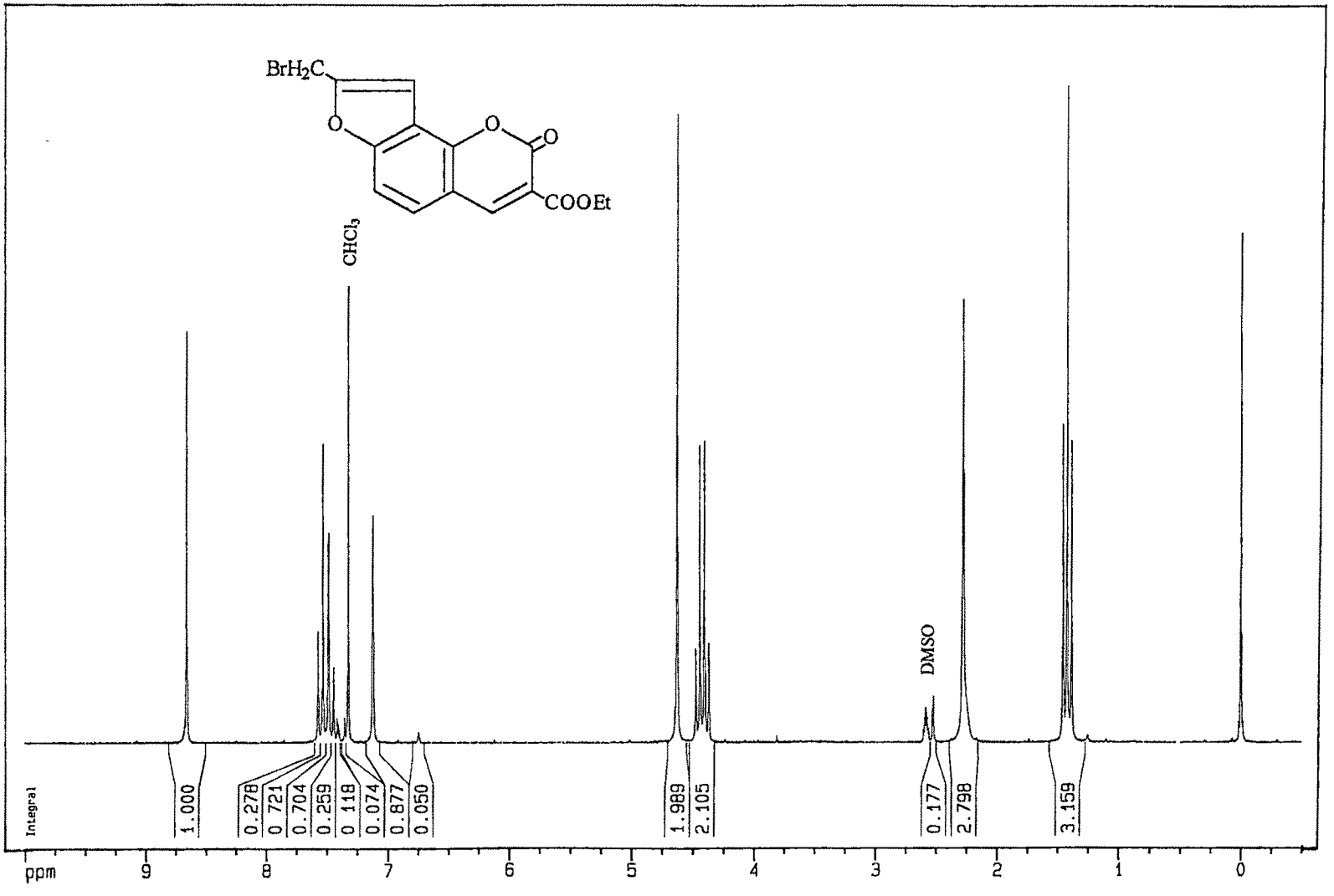

BrH2C
O
O
O
O
COOEt
CHCl3
DMSO
Integral
1.000
0.278
0.721
0.704
0.259
0.118
0.074
0.877
0.050
1.989
2.105
0.177
2.798
3.159
ppm
9
8
7
6
5
4
3
2
1
0

Fig. II.10

at 7.95. **[Fig. II.11]** It also suggests that the substitution of secondary amine has occurred not only at C-2 bromomethyl group but also at C-6 ester linkage.

The above reaction was also studied with 2 moles of N-bromosuccinimide under the same reaction conditions yielded exclusively bromomethylfurobenzopyrone.

In this reaction it was anticipated to give first a benzylic brominated product, which when treated with a base would yield the desired furobenzopyrone. Contrary to this, the reaction gave a mixture of furobenzopyrone and bromomethylfurobenzopyrone. This reveals that the initially formed benzylic brominated product could be loosing HBr molecule to produce furobenzopyrone without the participation of base. The formation of bromomethyl product clearly signifies further bromination of furobenzopyrone.

Alkali soluble ethyl-7-hydroxy-8-allylbenzopyran-2H-one-3-carboxylate (107), thus obtained by Claisen rearrangement was subjected to bromination with Br_2 in acetic acid, which gave ethyl-7-hydroxy-8-(2′,3′-dibromopropyl) benzopyran-2H-one-3-carboxylate (112). **[Scheme II.26]** Dehydrobromination of **112** was carried out by triethylamine in dry benzene, which gave a bromo isomer, identified by elemental analysis and PMR spectrum as ethyl-2-bromomethyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one-6-carboxylate (113). PMR signals in $CDCl_3$ at δ 1.40, a triplet for three methyl group protons of ester at C-6; two double doublet at 3.30 and 3.55 for each one proton at C-3; at 3.65 doublet for two methylene protons at C-2; a quartet at 4.40 for two methylene protons of ester at C-6; a multiplet at 5.25 for proton at C-2; two doublets at 6.80, J = 8.5Hz and δ 7.45, J = 8.5Hz for protons at C-9 and C-8 respectively and a singlet obtained at 8.40 for proton at C-7. **[Fig. II.12]**

Pardanani *et al.*[67] synthesized several linear furobenzopyrones by substituting either with -Br or -I at 8th position of coumarin ring system and thus subjected 7-allyloxy-8-iodo/bromocoumarins to Claisen rearrangement to obtain C-6 isomer followed by cyclization. In a similar way it was thought to

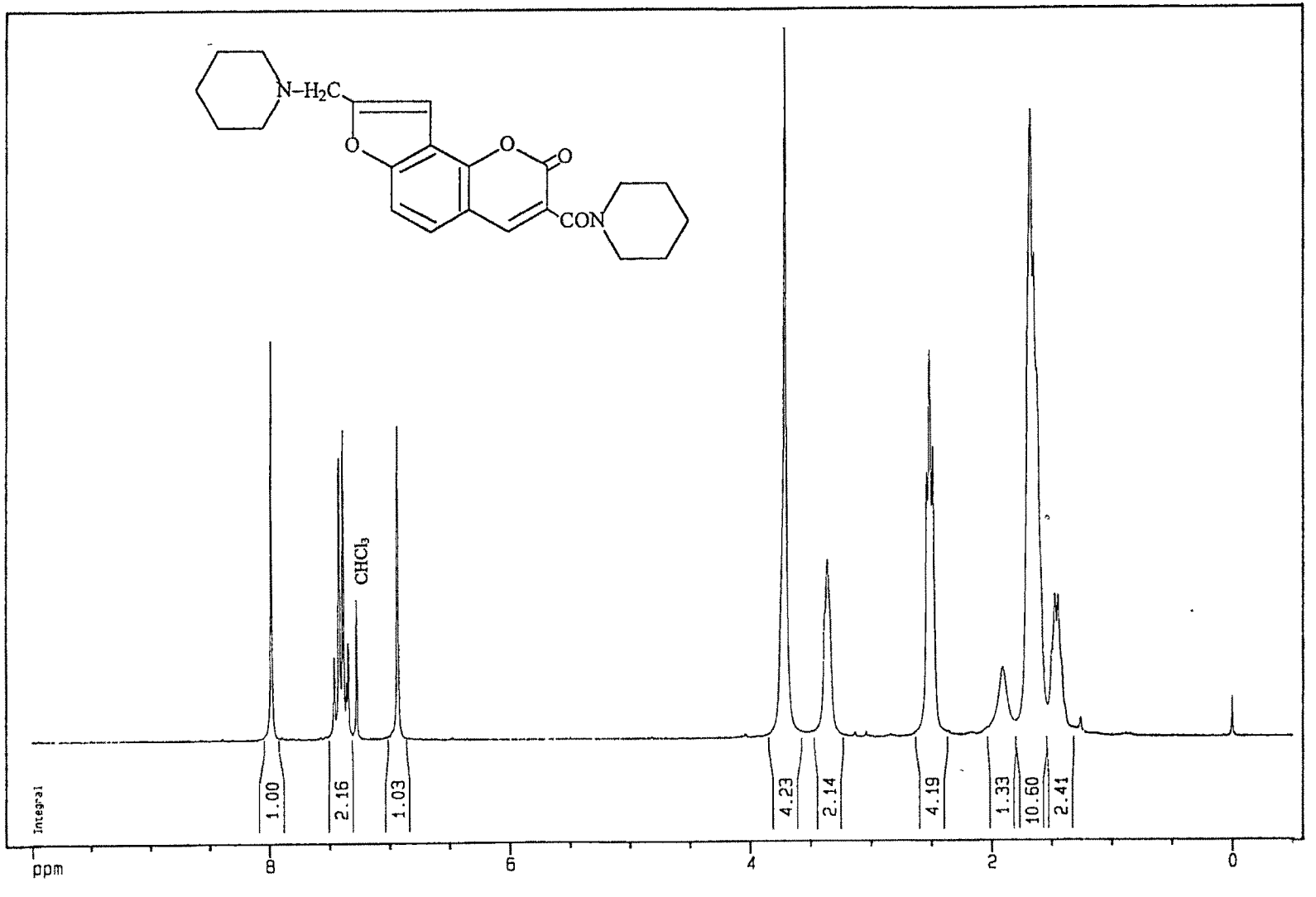
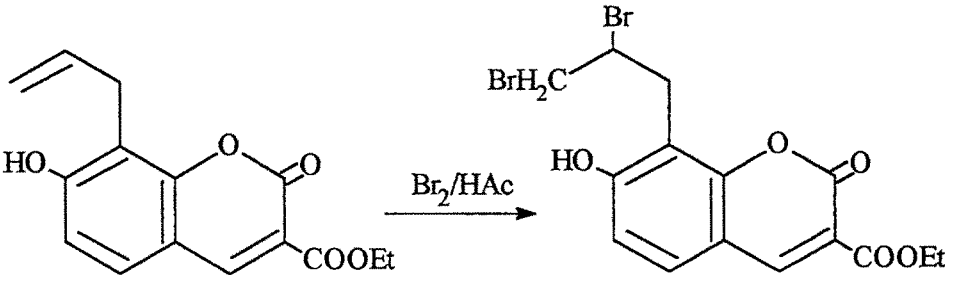
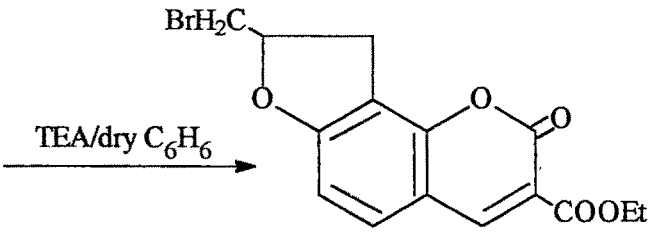

N–H2C
O
O
O
CON
CHCl3
Integral
1.00
2.16
1.03
4.23
2.14
4.19
1.33
10.60
2.41
ppm
8
6
4
2
0

Fig. II.11

Scheme II.26



107 112



113

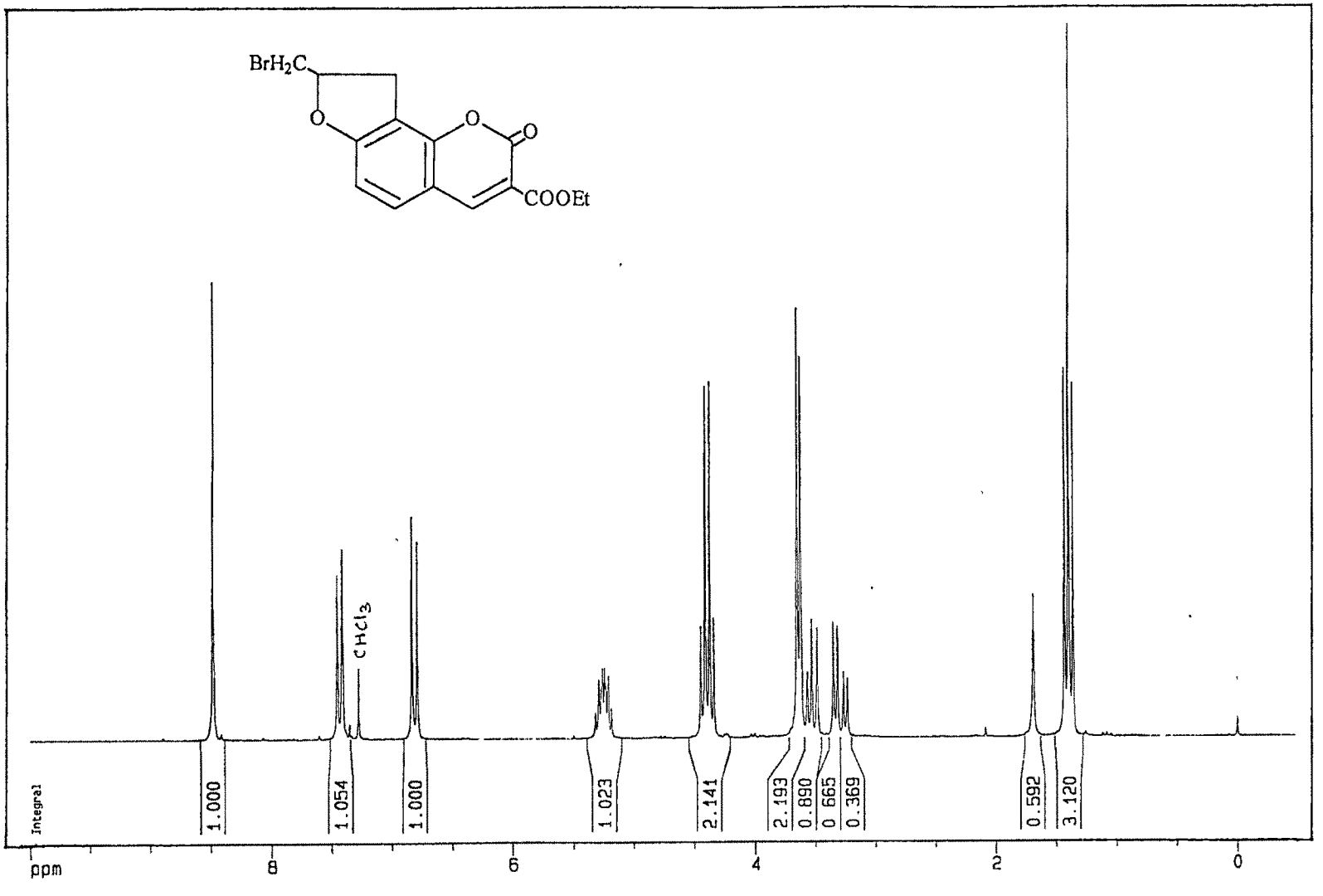

BrH2C
O
O
O
COOEt
CHCl3
Integral
1.000
1.054
1.000
1.023
2.141
2.193
0.890
0.665
0.369
0.592
3.120
ppm
8
6
4
2
0

Fig. II.12

synthesize linear furobenzopyrones with an electron withdrawing substituent at position 3.

Iodination of ethyl-7-hydroxybenzopyran-2H-one-3-carboxylate (105) was carried out by two conventional methods to obtain exclusively ethyl-7-hydroxy-8-iodobenzopyran-2H-one-3-carboxylate (114).

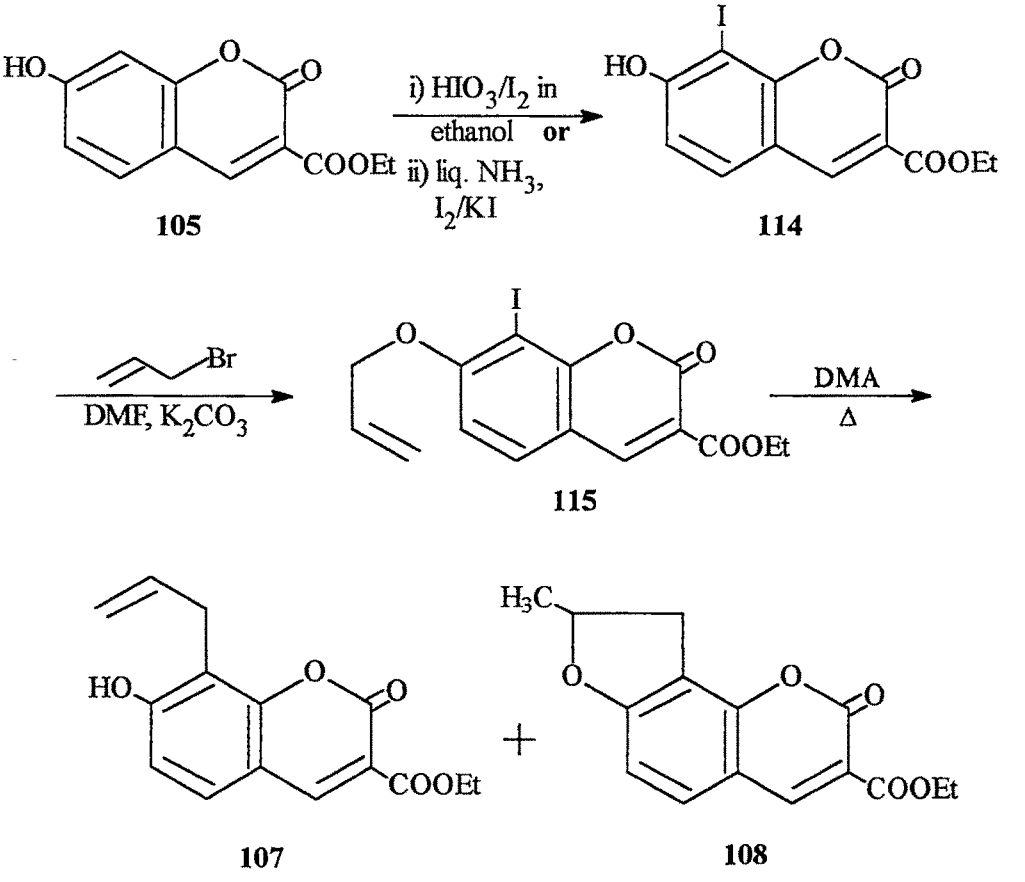
❶ by stirring equimolar mixture of iodic acid and iodine in alcohol with **105** at room temperature for 1h.

❷ by stirring **105** in ammonia with iodine solution for 1h and then working up in chilled dilute H_2SO_4.

The first method gave almost quantitative yield (85%), whereas the second method gave little lower yield (77%). The PMR spectrum of the product could not be taken due to poor solubility.

114 was allylated with allylbromide give ethyl-7-allyloxy-8-iodo benzopyran-2H-one-3-carboxylate (115). **[Scheme II.27]** Its structure was assigned by elemental analysis, IR spectrum in KBr at 1752 and 1690cm^{-1} due to >CO of lactone and ester **[Fig. II.13]** and the PMR spectrum in $CDCl_3$, which showed a triplet at δ 1.40 for three methyl protons of ester at C-3; a quartet at 4.40 for two methylene protons of ester at C-3; a doublet at 4.75 for two protons in allyloxy chain -$OC\underline{H}_2CH{=}CH_2$ at C-7; two multiplets obtained at 5.35-5.65 and 6.05 for three protons of -$OCH_2CH{=}C\underline{H}_2$ and -$OCH_2C\underline{H}{=}CH_2$ at C-7 respectively; two doublets at 6.85, J = 9Hz and 7.55, J = 9Hz for each one proton at C-6 and C-5 and a singlet for one proton of C-4 at 8.40. **[Fig. II.14]** Signals appeared at δ 6.85 and 7.55 for two ortho coupled protons clearly indicates that there is no substitution at C-6 and C-5 and the absence of signal at C-8 proton confirms that the iodine got substituted at C-8. **115** was then subjected to Claisen rearrangement in N,N-DMA, produced a mixture of two products as alkali soluble and alkali insoluble. Alkali soluble product was isolated by stirring the crude reaction mixture with dilute alkali

Scheme II.27


HO
O
O
COOEt
105
i) HIO_3/I_2 in ethanol or ii) liq. NH_3, I_2/KI
I
HO
O
O
COOEt
114
Br
DMF, K_2CO_3
I
O
O
O
COOEt
115
DMA
Δ
HO
O
O
COOEt
107
+
H_3C
O
O
O
COOEt
108

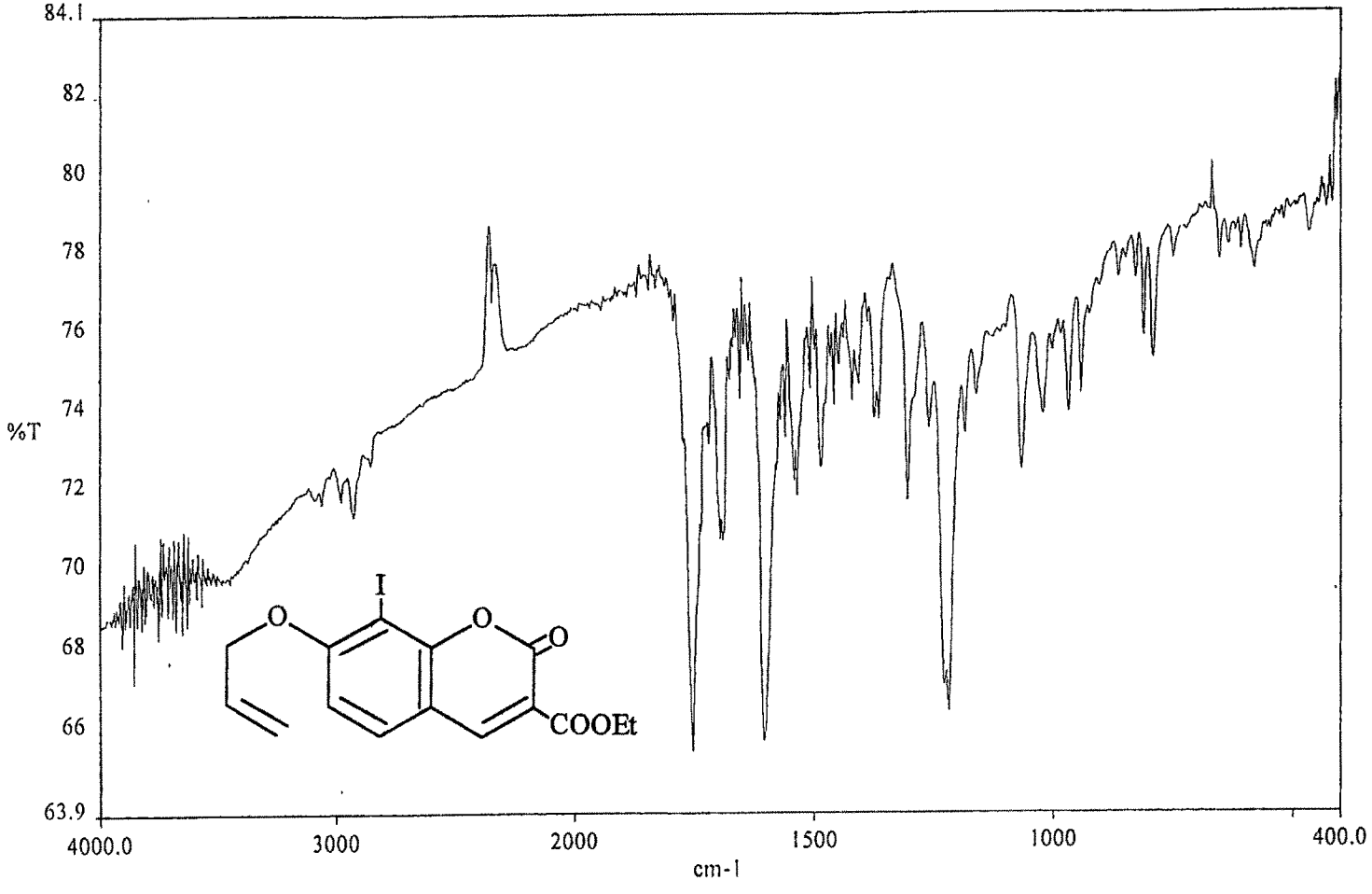

84.1
82
80
78
76
74
72
70
68
66
63.9
%T
4000.0
3000
2000
1500
1000
400.0
cm-1
I
O
O
O
COOEt

Fig. II.13

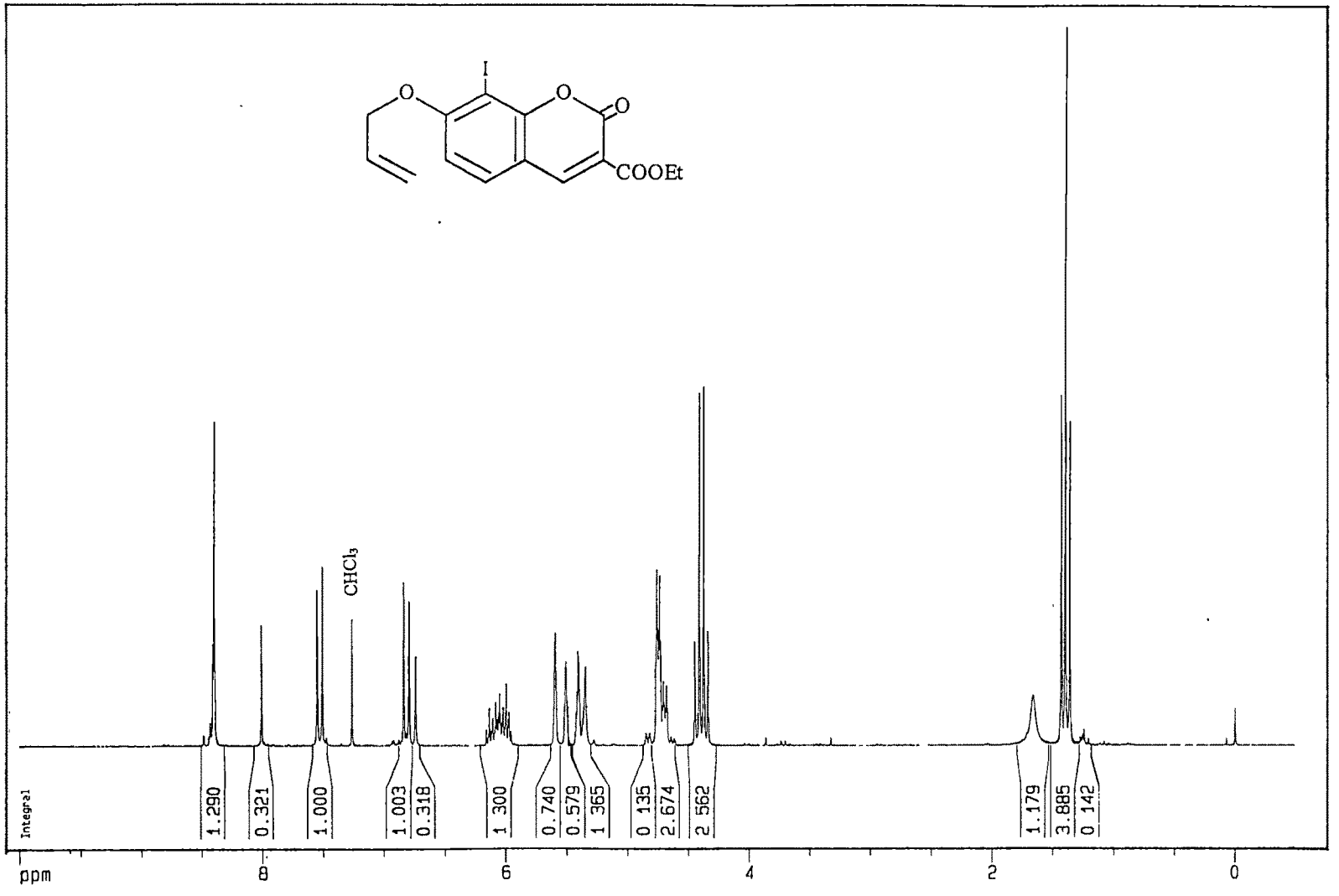

I
O
O
O
COOEt
CHCl3
Integral
1.290
0.321
1.000
1.003
0.318
1.300
0.740
0.579
1.365
0.135
2.674
2.562
1.179
3.885
0.142
ppm
8
6
4
2
0

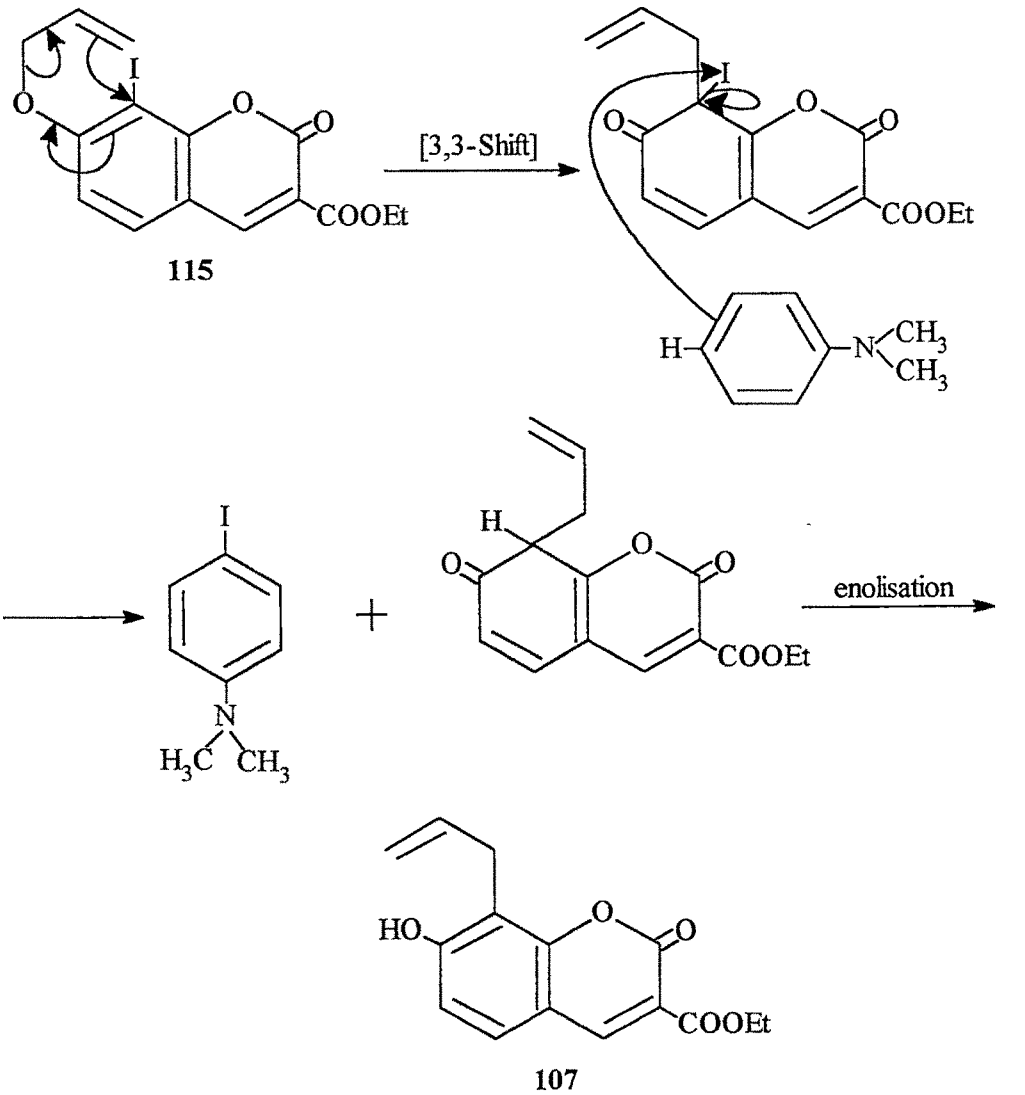
Fig. II.14

and identified as ethyl-7-hydroxy-8-allylbenzopyran-2H-one-3-carboxylate (107). In a similar way the alkali insoluble product was identified as ethyl-2-methyl-2,3-dihydrofuro(2,3h)benzopyran-5H-one-6-carboxylate (108). Structures of both the products were confirmed from their elemental analysis, mmp with earlier compounds **107**, **108** and by PMR spectra. A plausible mechanism for the formation of **107** is given in **Scheme II.28**.

The above strategy was successfully reported to synthesize linear furo derivatives by Desai *et al.*[68], Patel *et al.*[69] for coumarins and xanthons. It was only unsuccessful as reported by Joshi *et al.*[70] in case of 7-allyloxy-8-Br/I isoflavone. The failure here could be attributed mainly due to the presence of an electron withdrawing substituent at position 3 in the 7-hydroxycoumarin system. The mechanism for the formation of ethyl-7-hydroxy-8-allyl benzopyran-2H-one-3-carboxylate (107) is given.

2-Methyl-6-acetylfuro(2,3-h)benzopyran-5H-one (120) was prepared by first subjecting 7-hydroxy-3-acetylbenzopyran-2H-one (116) to allylation, gave 7-allyloxy-3-acetyl benzopyran-2H-one (117). Very poor yield was observed again as in the case of carboxylate, when dry acetone was used as a solvent for allylation. Subsequent Claisen rearrangement of **117** in refluxing DMA yielded a mixture of two isomers, alkali soluble and alkali insoluble. The crude reaction mixture was then treated with dilute alkali to separate the alkali soluble product, which was identified as 7-hydroxy-8-allyl-3-acetylbenzopyran-2H-one (118) from elemental analysis as well as PMR spectrum. The alkali insoluble part was recrystallized and the structure was confirmed on the basis of its elemental analysis and PMR data as 2-methyl-6-acetyl-2,3-dihydrofuro(2,3-h) benzopyran-5H-one (119). **[Scheme II.29]** **119** on dehydrogenation with Pd/C (10%) in refluxing diphenylether for about 6 to 24h and DDQ in dry benzene or dioxane for 24h, did not give required product 2-methyl-6-acetylfuro(2,3-h)benzopyran-5H-one (120), but only the starting material was recovered.

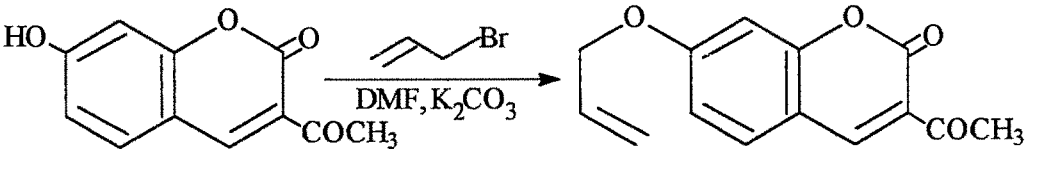
Scheme II.28



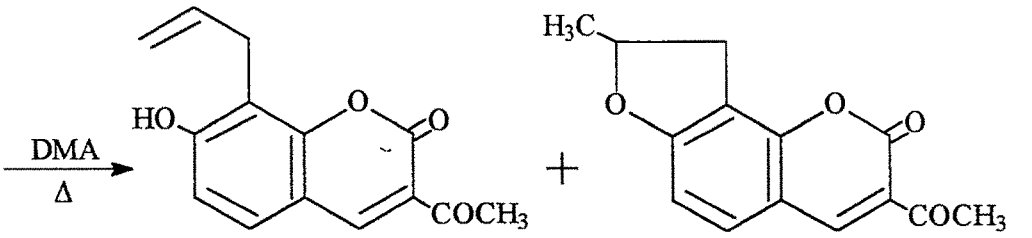
115

107

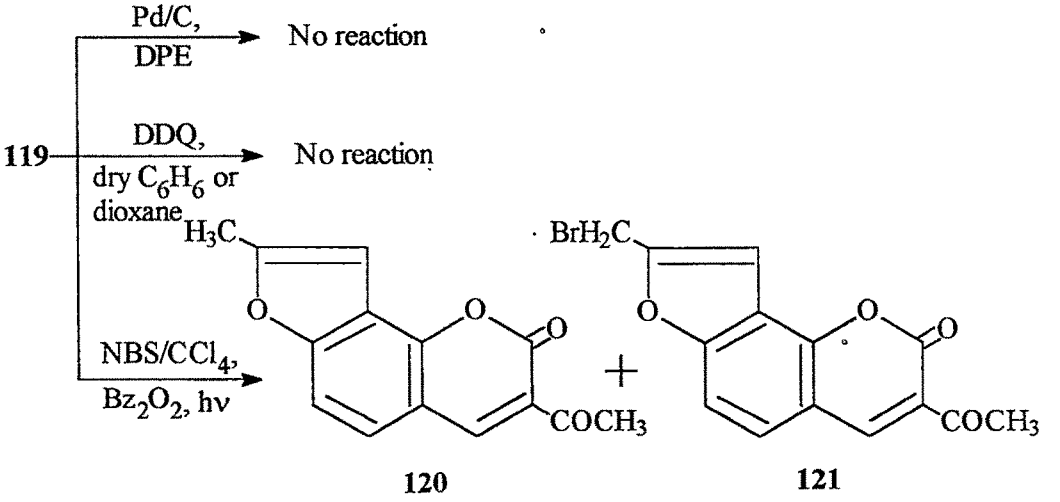
Scheme II.29



116 **117**



118 **119**



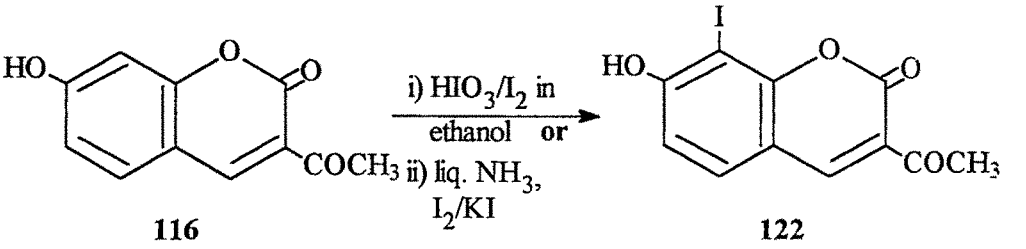
120 **121**

As the above methods failed to undergo dehydrogenation, **119** was treated with NBS in the presence of benzoyl peroxide using chloroform as solvent resulted in the formation of a mixture of two products, which were isolated by fractional crystallization. The structures of the products were assigned by their elemental analysis and PMR spectra as 2-methyl-6-acetylfuro (2,3-h)benzopyran-5H-one (120) and 2-bromomethyl-6-acetylfuro (2,3-h)benzopyran-5H-one (121). The above reaction when carried out with 2 moles of NBS under the same reaction conditions produced exclusively bromomethylfurobenzopyrone. Formation of these two products further supports the dehydrogenation of dihydrofuro derivative using NBS.

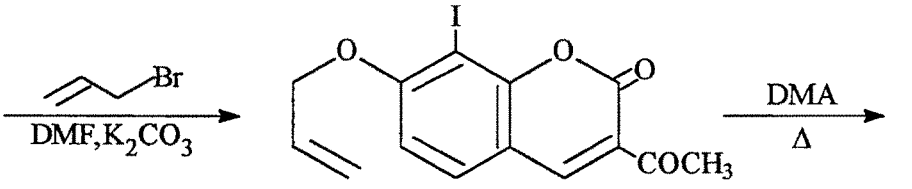
Iodination of **116** was carried out by HIO_3 as well as by ammonia as described earlier in the Scheme II.27. PMR spectrum of the product 7-hydroxy-8-iodo-3-acetylbenzopyran-2H-one (122) could not be taken due to poor solubility. **122** on allylation with allylbromide gave 7-allyloxy-8-iodo-3-acetyl benzopyran-2H-one (123). **[Scheme II.30]** Its structure was confirmed by elemental analysis and PMR data. **123** when attempted to Claisen rearrangement, afforded a mixture of two products as alkali soluble and alkali insoluble. Alkali soluble product was isolated by stirring the crude reaction product with dilute alkali and identified as 7-hydroxy-8-allyl-3-acetyl benzopyran-2H-one (118). Similarly alkali insoluble product was assigned 2-methyl-6-acetyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one (119). Structures of both the products were confirmed by their elemental analysis, TLC comparison and mmp with earlier products **118, 119.**

Synthesis of ethyl-2,9-dimethylfuro(3,2-g)benzopyran-7H-one-6-carboxylate (127) was achieved by subjecting 2,6-dihydroxytoluene to Knoevenagel condensation of with diethylmalonate to give ethyl-7-hydroxy-8-methylbenzopyan-2H-one-3-carboxylate (124), which on allylation produced ethyl-7-allyloxy-8-methylbenzopyran-2H-one-3-carboxylate (125). **125** on

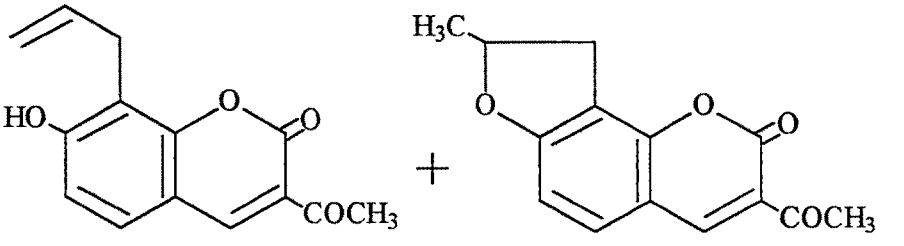
Scheme II.30



116 122



123



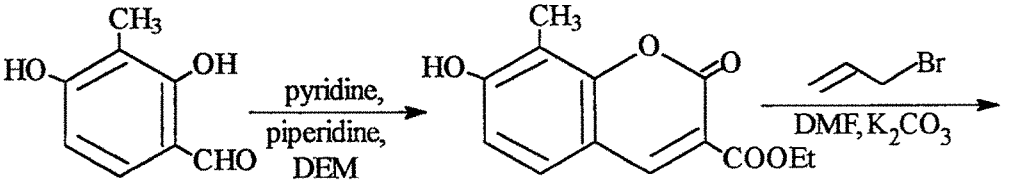
118 119

subsequent Claisen rearrangement in refluxing DMA afforded a crude solid, which was stirred with dilute alkali and acidified with HCl to give the product **126**. **[Scheme II.31]** The structure of the product was assigned on the basis of elemental analysis, IR in KBr and PMR in $CDCl_3$ as ethyl-7-hydroxy-6-allyl-8-methylbenzopyran-2H-one-3-carboxylate (126). IR showed a broad band for hydroxyl group at 3378cm^{-1} and two bands at 1735 and 1702cm^{-1} for >CO of lactone and ester respectively. **[Fig. II.15]** It showed signals in PMR at δ 1.40, a triplet for three methyl group protons of ester at C-3; a singlet at 2.30 for three methyl group protons at C-8; a doublet at 3.45 for two methylene protons of $-CH_2-CH=C\underline{H}_2$ at C-6; a quartet at 4.40 for two methylene protons of ester at C-3; two multiplets at 5.10 and 6.00 of methylene protons of $-CH_2-CH=C\underline{H}_2$ and a proton of $-CH_2-C\underline{H}=CH_2$ at C-6 and two singlets at 7.20 and 8.45 for each one proton at C-5 and C-4 respectively. **[Fig. II.16]**

Cyclization and dehydrogenation of the above product was not attempted by normal methods such as bromination followed by cyclization with alcoholic KOH or cyclization with conc. H_2SO_4 and then dehydrogenation, due to the possible hydrolysis of the ester linkage, instead an alternative method was adopted.

126 on oxypalladation with $PdCl_2$ and freshly prepared CuCl using a mixture of DMF:H_2O as a medium under oxygen atmosphere afforded exclusively linear furobenzopyrone **127** rather than acetonyl derivative. The structure of the product ethyl-2,9-dimethylfuro(3,2-g)benzopyran-7H-one-6-carboxylate (127) was confirmed by its elemental analysis, IR and PMR. Its IR spectrum in KBr exhibited two bands at 1762 and 1702cm^{-1} for >CO of lactone and ester **[Fig. II.17]** while the PMR spectrum in $CDCl_3$ showed signals at δ 1.40, a triplet for three methyl group protons of ester at C-6; a singlet at 2.40 for three methyl group protons at C-9; a singlet at 2.50 for three methyl group protons at C-2; a quartet at 4.40 for two methylene protons of ester at C-6; two

Scheme II.31



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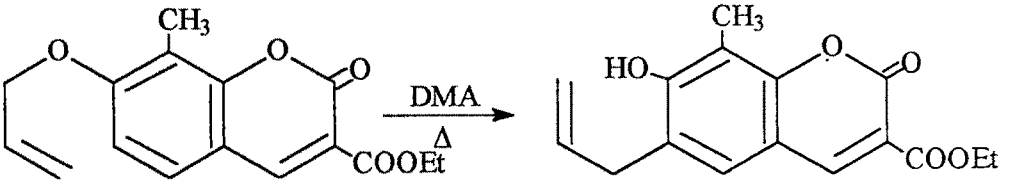
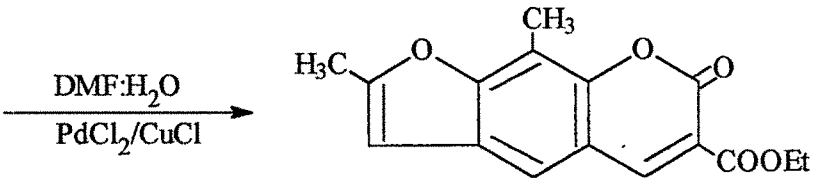
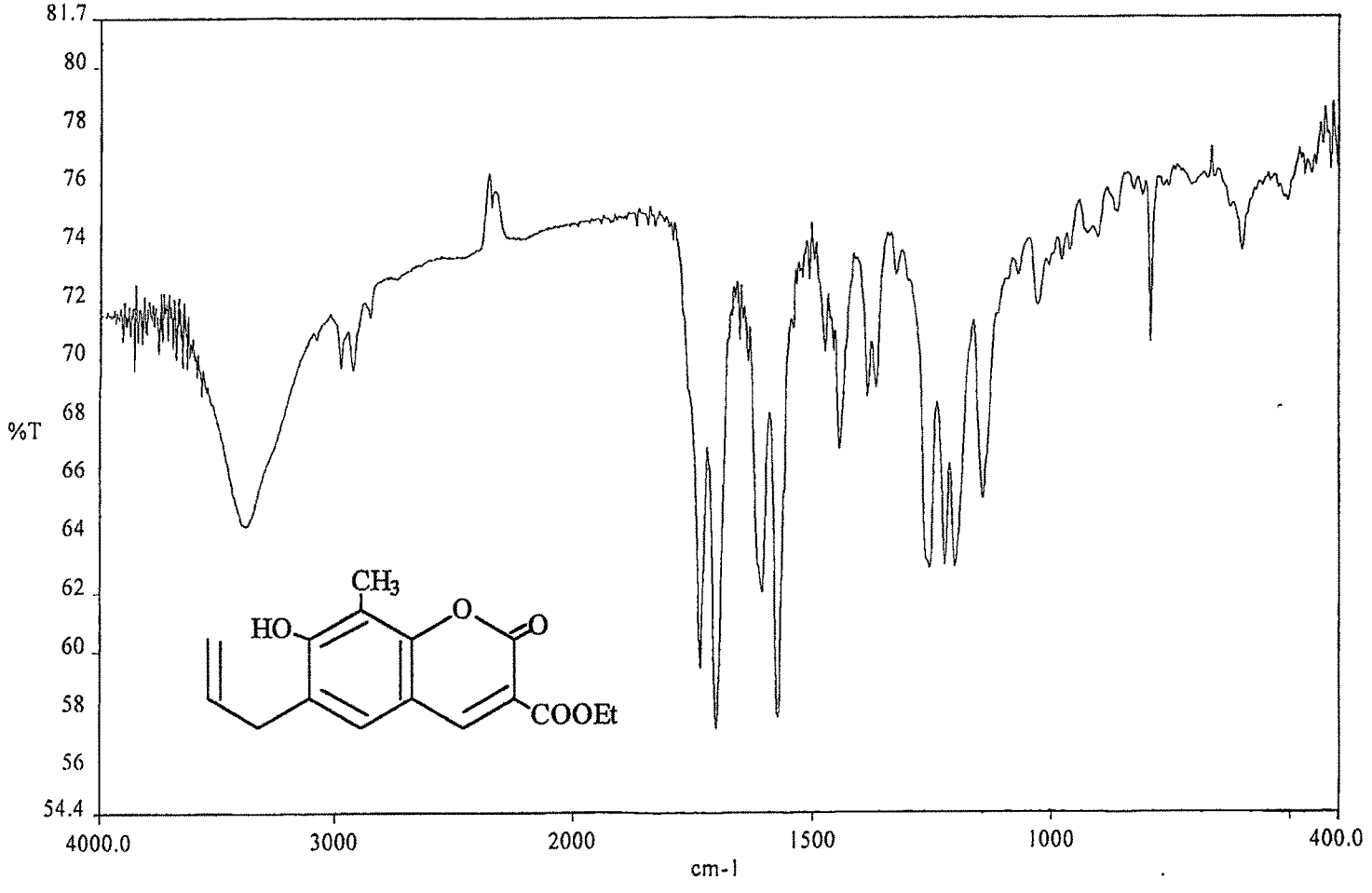


125 **126**



127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74
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62
60
58
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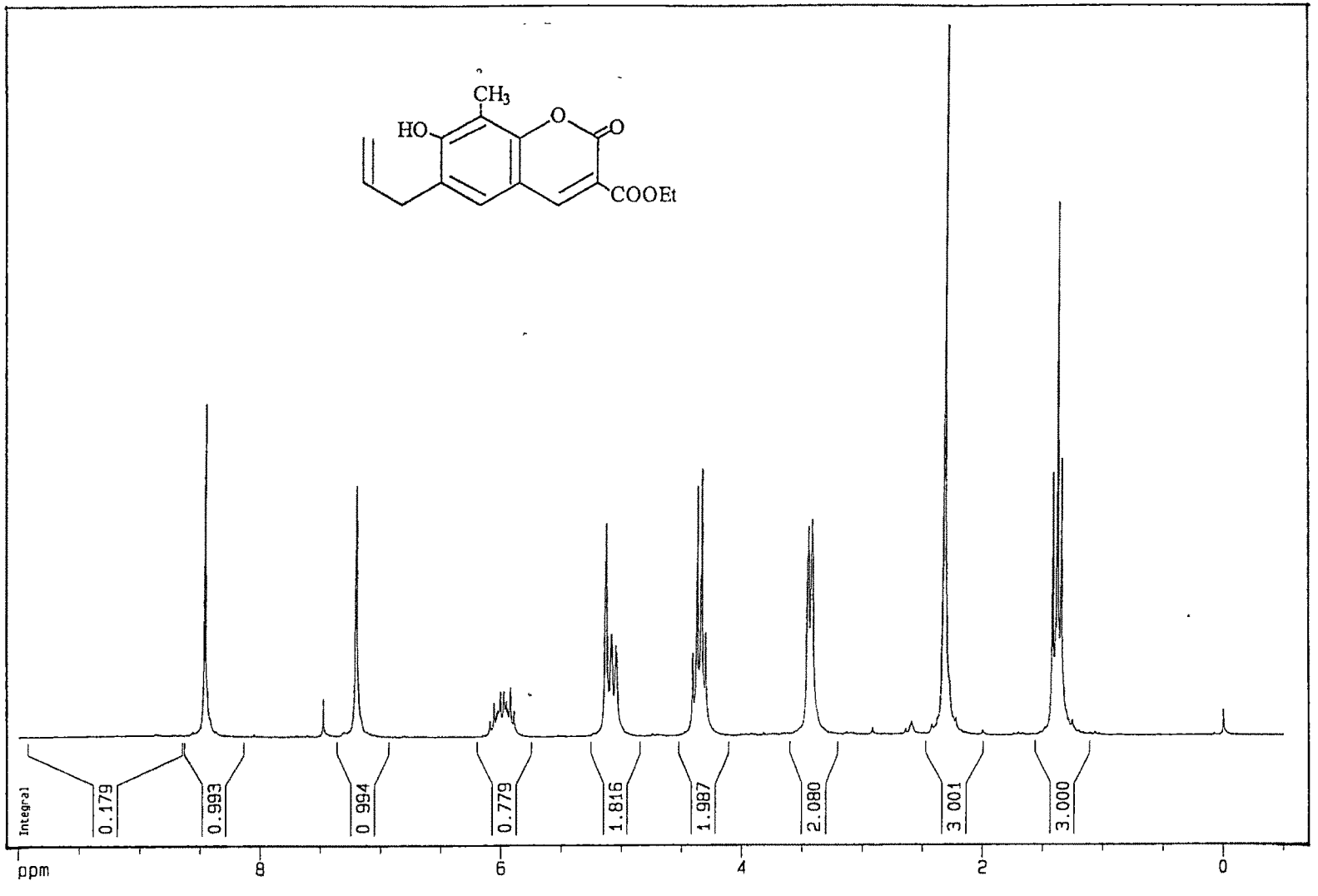
1500
1000
400.0
cm-1
CH3
HO
O
O
COOEt

Fig. II.15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COOEt
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0.993
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0.779
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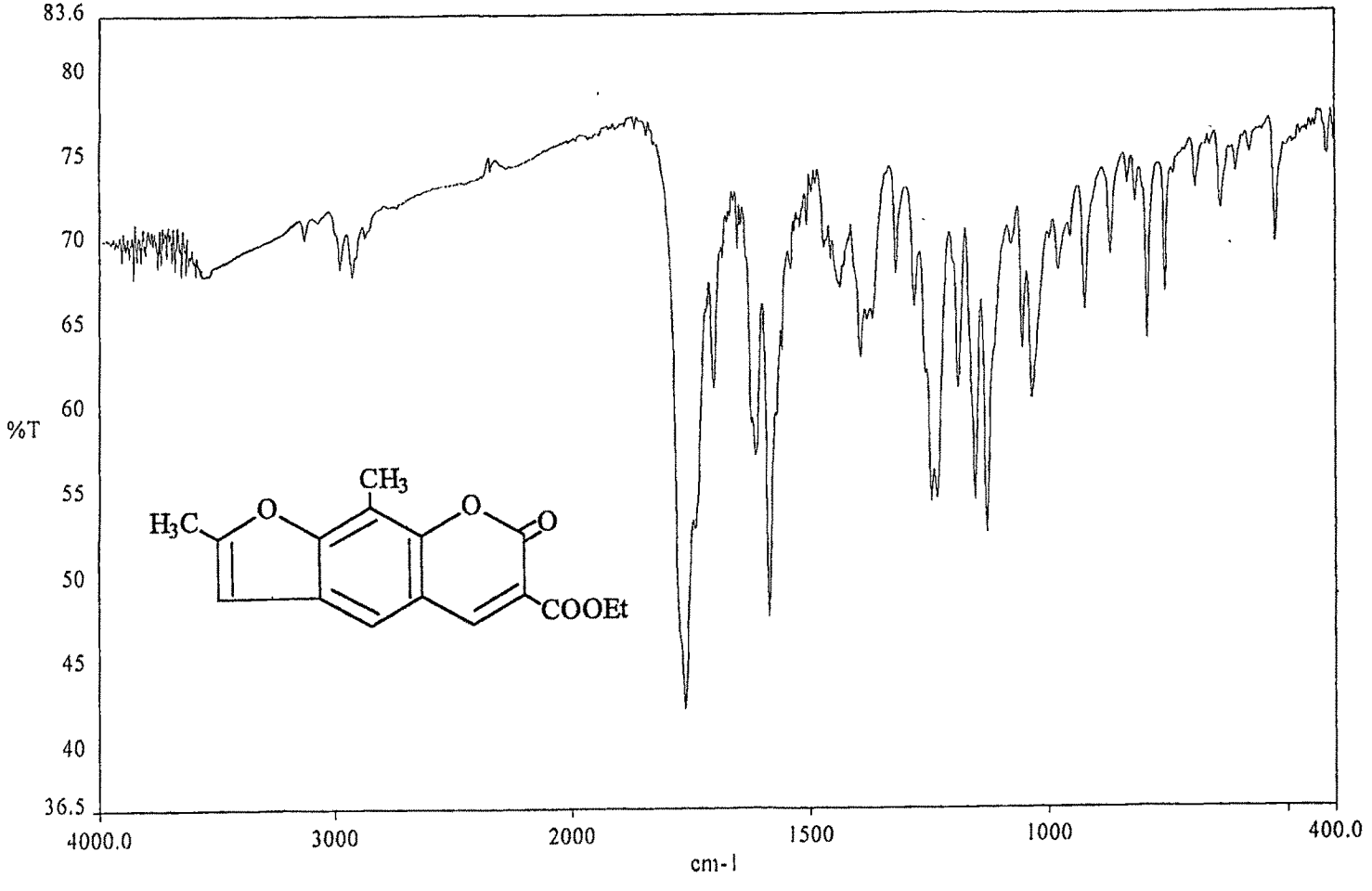
1.987
2.080
3 001
3.000
ppm
8
6
4
2
0

Fig. II.16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36.5
%T
4000.0
3000
2000
1500
1000
400.0
cm-1
CH3
H3C
O
O
O
COOEt

Fig. II.17

singlets at 6.40 and 7.35 for each one proton at C-3 and C-4 respectively and another singlet at 8.50 for proton at C-5. **[Fig. II.18]**

As above, in a similar way it was planned to prepare 7-hydroxy-3-cyano-benzopyran-2H-one by Knoevenagel condensation using ethylcyanoacetate followed by allylation, Claisen rearrangement and dehydrogenation.

2,4-Dihydroxybenzaldehyde when allowed to condense with ethylcyanoacetate in the presence of piperidine using dry pyridine as solvent gave a high melting product, which could not be purified due to poor solubility. It was also attempted in a similar way as reported by Yasuda *et al.*[71] by condensing 4-acetoxy-2-hydroxybenzaldehyde and ethylcyanoacetate with few drops of piperidine, gave an 2-imino-3-ethoxycarbonyl-2H-chromene.

Contrary to the above methods, Nakai *et al.*[72] and Srinivas *et al.*[73] who used malononitrile to synthesize the desired product by using zinc chloride or piperidine in good yields, was also not successful in making the 7-hydroxy-3-cyanobenzopyran-2H-one. Therefore a different strategy was envisaged in which 2,4-dihydroxybenzaldehyde would be allylated first followed by Knoevenagel condensation.

2,4-Dihydroxybenzaldehyde was first allylated with allylbromide in presence of K_2CO_3 and dry acetone afforded a liquid mixture of mono- and di-allyloxybenzaldehyde (128, 129). Knoevenagel condensation with ethylcyano-acetate in presence of piperidine and pyridine as solvent, which gave a mixture of two products, were isolated by column chromatography. Open chain product was eluted out in petroleum ether as bright yellow needles and the second product in a mixture of petroleum ether and benzene (50:50) as pale orange needles. **[Scheme II.32]** The structure of both the products were identified on the basis of elemental analysis, IR and PMR data as ethyl-2,4-diallyloxy-α-cyanocinnamate (130) and 7-allyloxy-3-cyanobenzopyran-2H-one (131). **130** exhibited characteristic bands for cyano at 2220 and for >CO of ester at 1703cm^{-1} in IR spectrum **[Fig. II.19]** while the PMR spectrum in $CDCl_3$

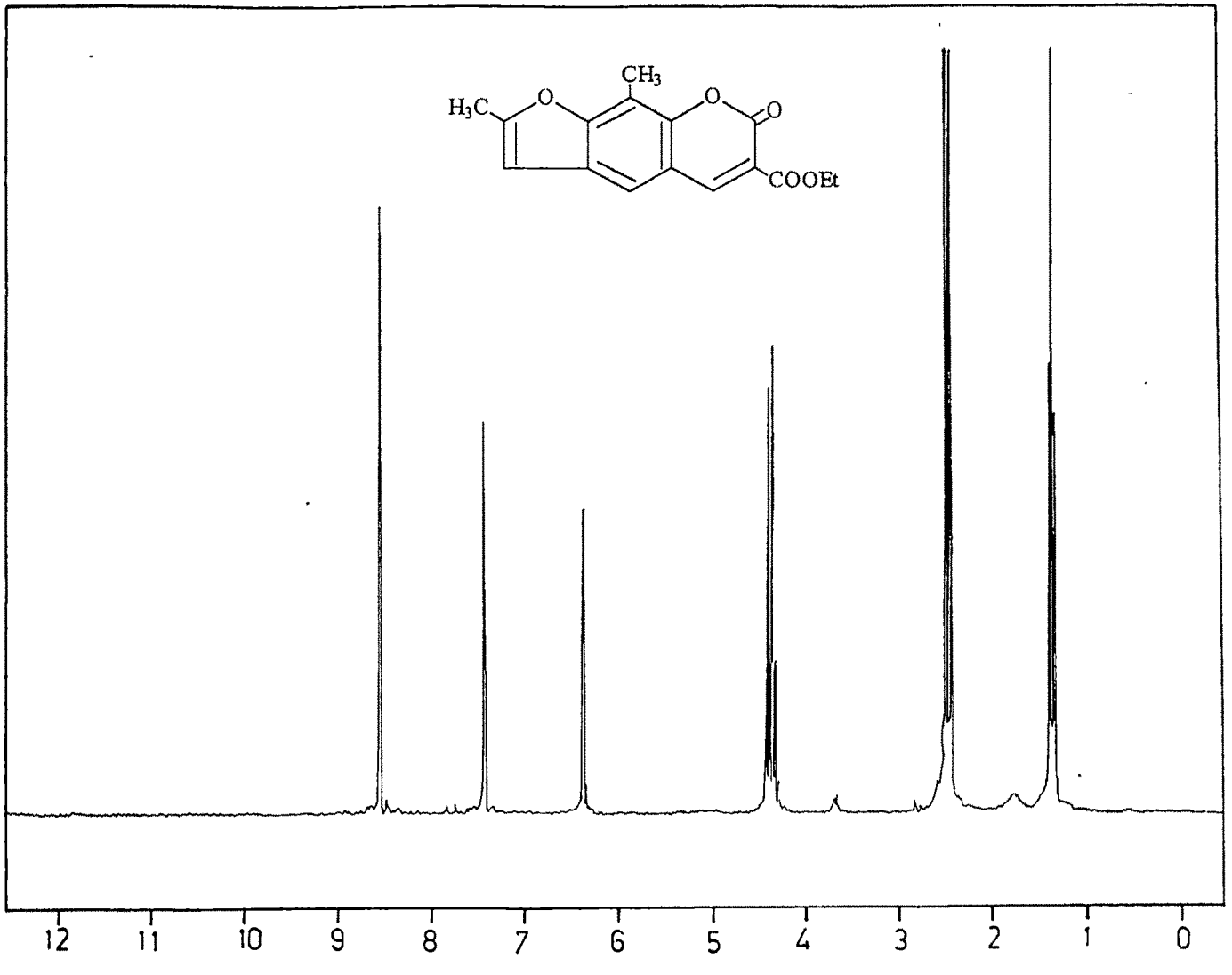
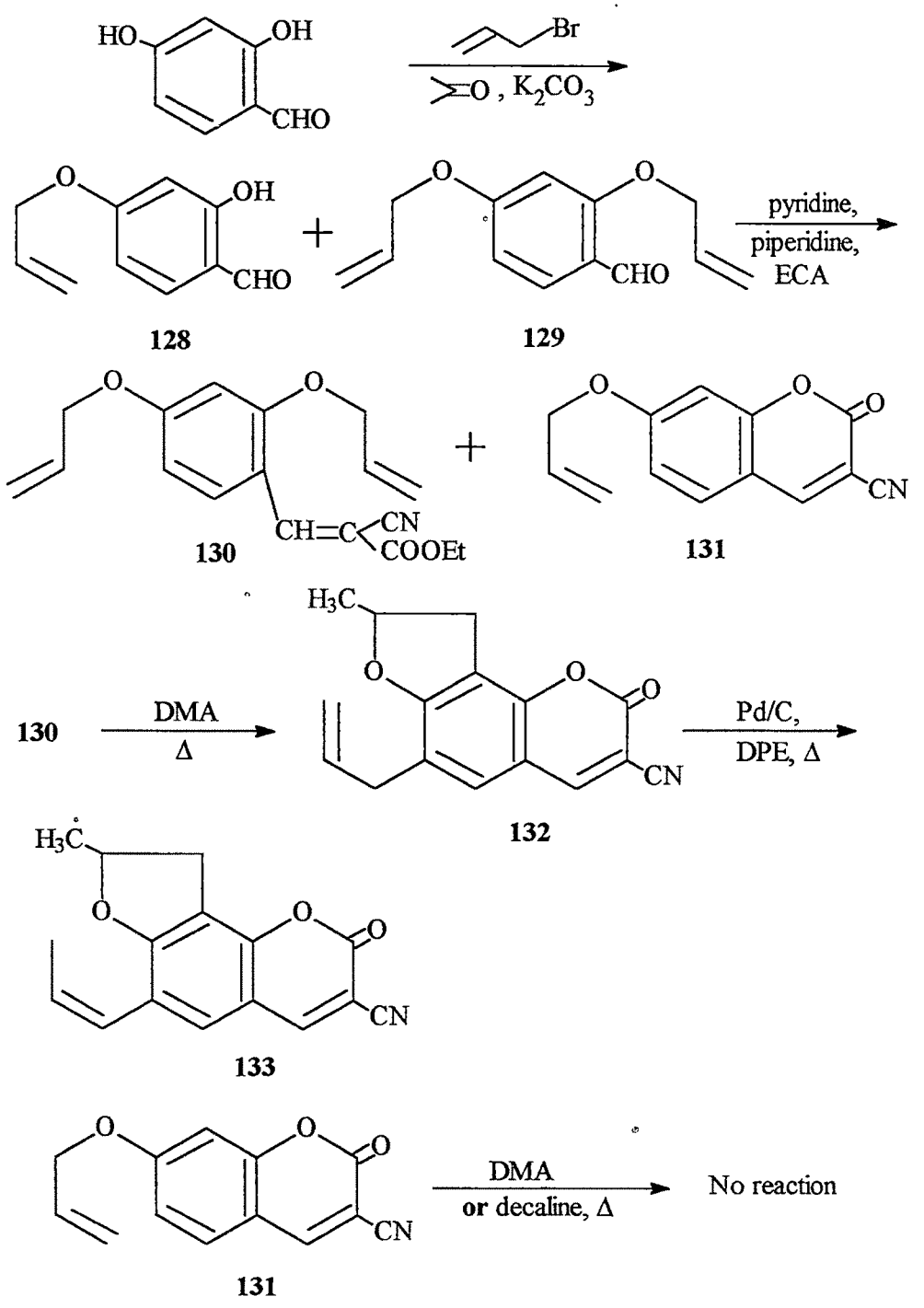


Fig. II.18

Scheme II.32


HO
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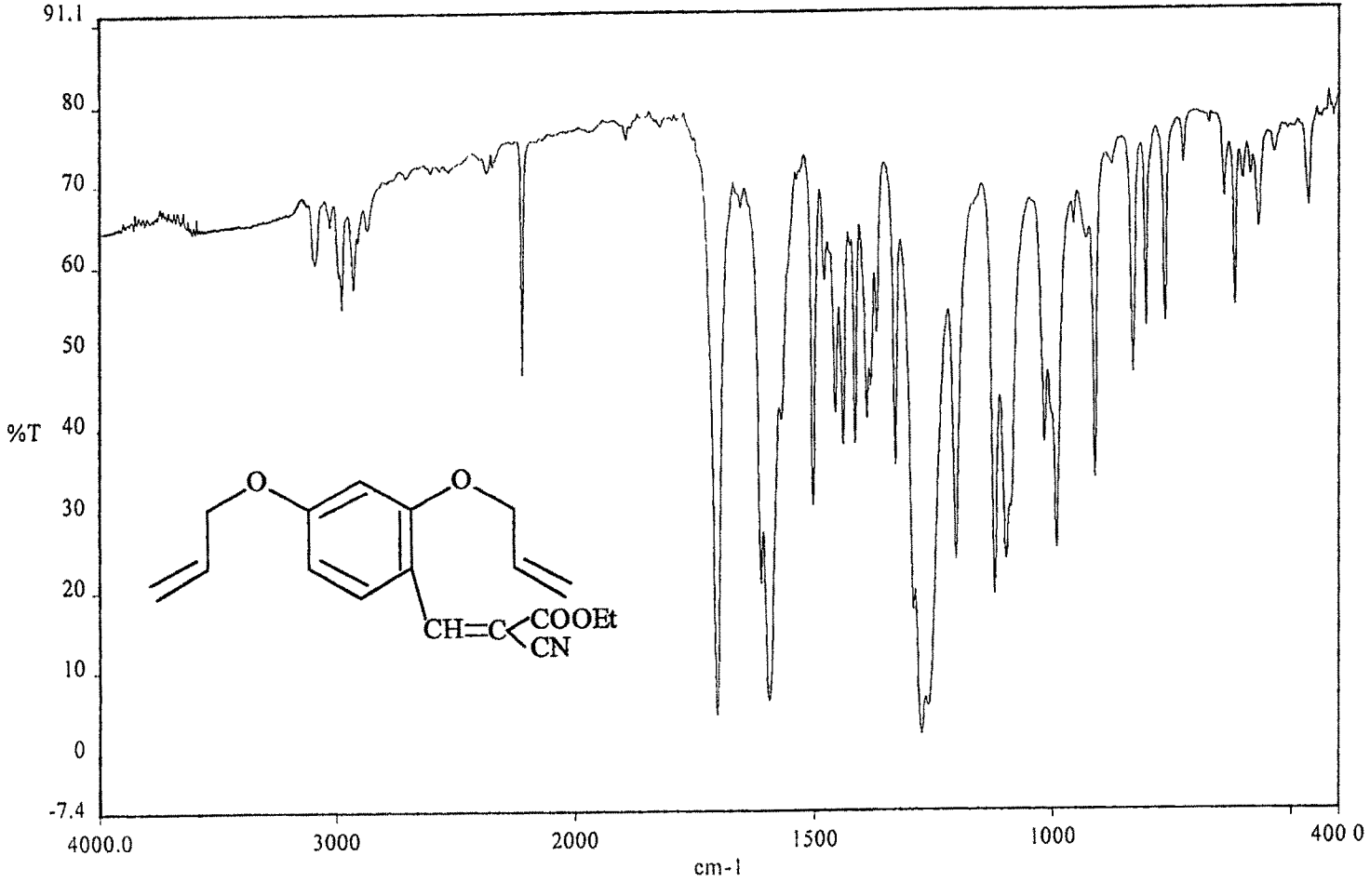
CHO
Br
=O , K_2CO_3
O
OH
CHO
+
O
O
CHO
pyridine,
piperidine,
ECA
128
129
O
O
CH=C
CN
COOEt
130
+
O
O
O
CN
131
H_3C
O
O
O
CN
130
DMA
Δ
Pd/C,
DPE, Δ
132
H_3C
O
O
O
CN
133
O
O
O
CN
131
DMA
or decaline, Δ
No reaction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70
60
50
%T 40
30
20
10
0
-7.4
4000.0
3000
2000
1500
1000
400 0
cm-1
O
O
CH=C
COOEt
CN

Fig. II.19

showed signals at δ 1.40, a triplet for three methyl group protons in ester group; a quartet at 4.30 for two methylene protons in ester group; a doublet at 4.55 for four protons of two $-CH_2-$ in $-OC\underline{H}_2CH=CH_2$; two multiplets at 5.30 and 5.95 for four protons of two $-CH_2-$ in $-OCH_2CH=C\underline{H}_2$ and two protons of two -CH- in $-OCH_2C\underline{H}=CH_2$ respectively; another multiplet at 6.50 for two protons at C-3 and C-5, doublet appeared at 8.35, J = 9Hz for proton at C-6 and a singlet at 8.55 for proton of β-carbon in the cinnamyl chain. **[Fig. II.20]**

The geometry of the compound is difficult to determine in this case as all the groups attached to the carbons are different. It could be explained to some extent the geometry first on the basis of down field shift of proton at β-carbon unusually to δ 8.55[74] and secondly by observing the yields. It was reported that when such compounds are subjected to cyclization, the yields are good in E-configuration due to less steric hindrance in comparison to Z-isomer. Looking at both these aspects i.e. down field shift and good yields of the products, the geometry of the product could probably be E.

131 exhibited characteristic bands for cyano and >CO of lactone at 2232 and 1741cm^{-1} in IR spectrum **[Fig. II.21]** while its PMR in DMSO showed signals at δ 4.70, doublet for two methylene protons of $-OC\underline{H}_2CH=CH_2$ at C-7; multiplet at 5.15-5.55 for two terminal methylene protons of $-OCH_2CH=C\underline{H}_2$ at C-7; another multiplet at 6.05 for a proton of $-OCH_2C\underline{H}=CH_2$; a multiplet at 7.00 for two protons at C-6 and C-8; doublet at 7.65 for proton at C-5 and a singlet appeared at 8.65 for a proton at C-4. **[Fig. II.22]** **131** was also subjected to Claisen rearrangement in refluxing DMA and decalin for a long time ranging between 7 to 24h failed to give the product, which is suggestive that the rearrangement of allyl group when a cyano group is present at position 3 in 7-hydroxycoumarin system does not proceed.

A facile synthesis of 9-allyl-6-cyano-2-methyl-2,3-dihydrofuro(2,3-h) benzopyran-5H-one (133) was carried out from **130**, which on Claisen rearrangement in refluxing DMA afforded a product **132**. Its structure was established from its elemental analysis, IR and PMR spectrum as 9-allyl-6-

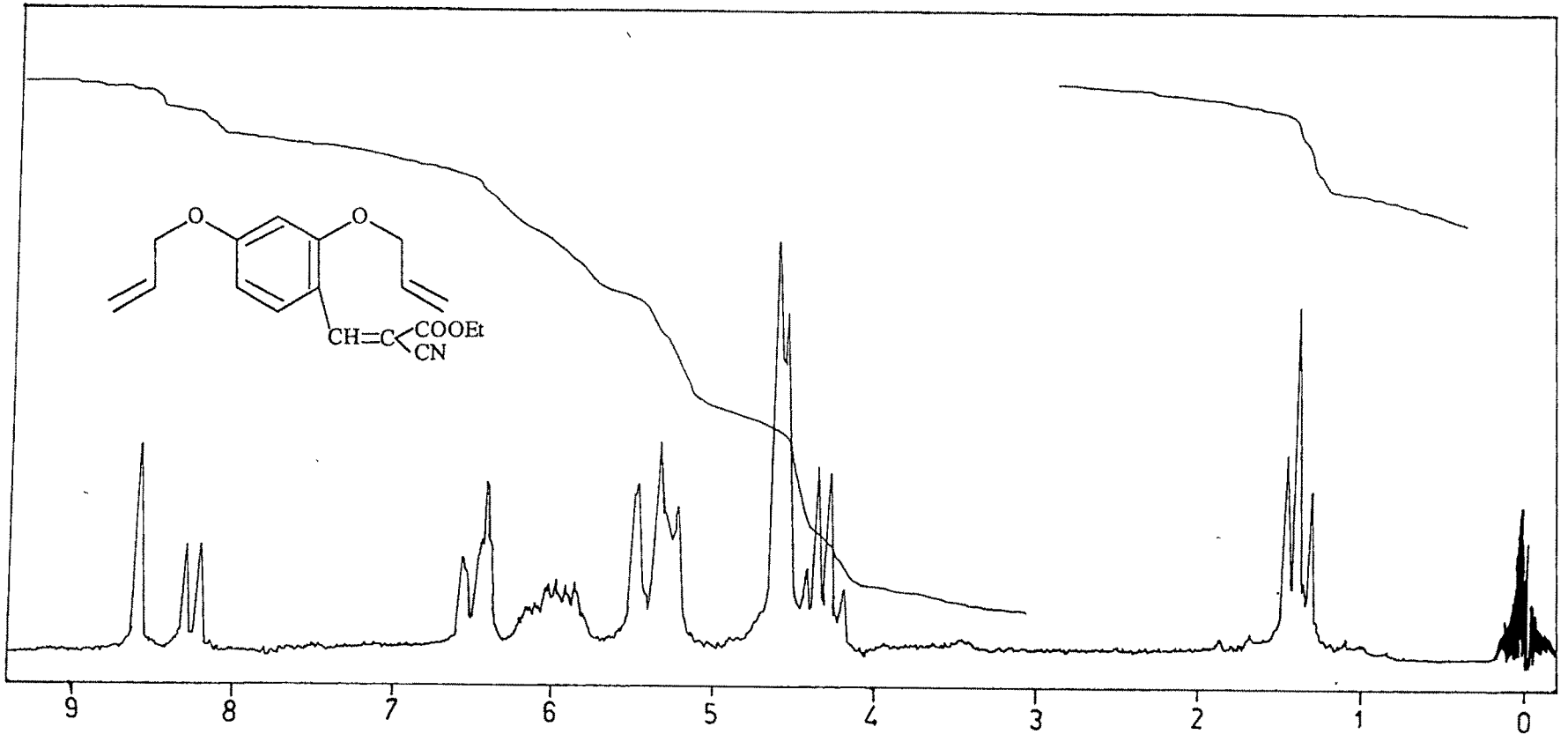
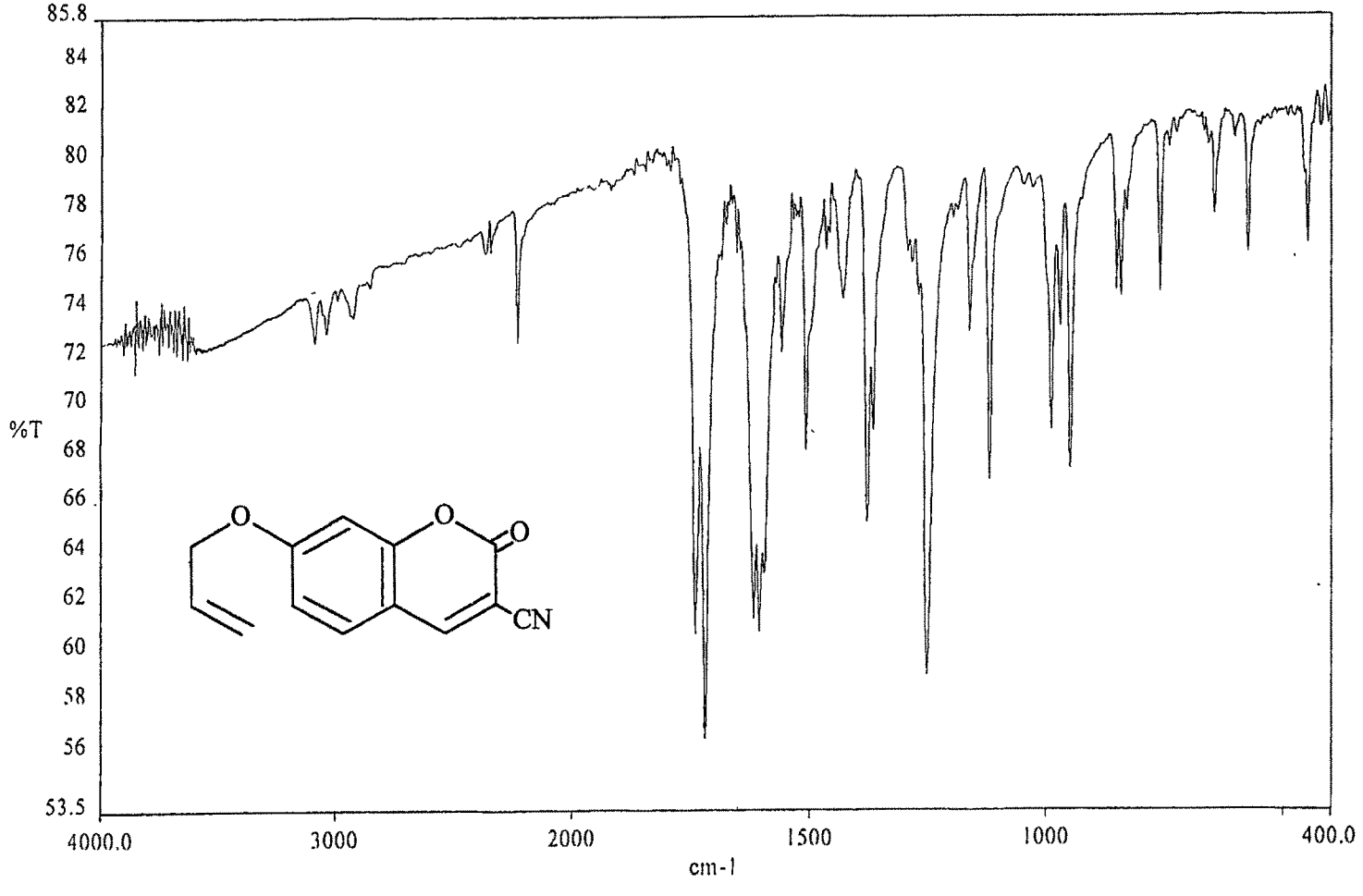


Fig. II.20


85.8
84
82
80
78
76
74
72
70
%T
68
66
64
62
60
58
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3000
2000
1500
1000
400.0
cm-1
O
O
O
CN

Fig. II.21

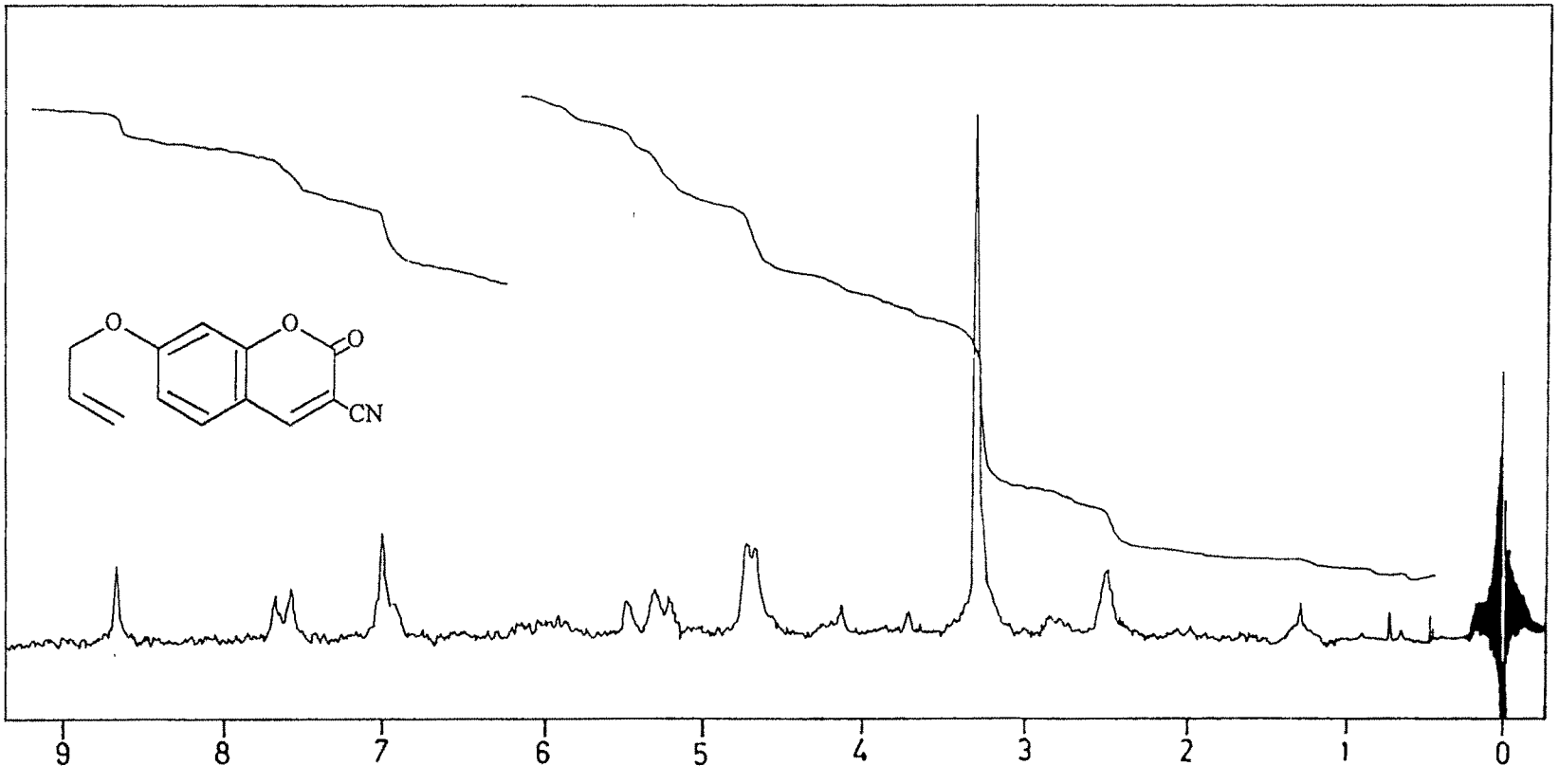
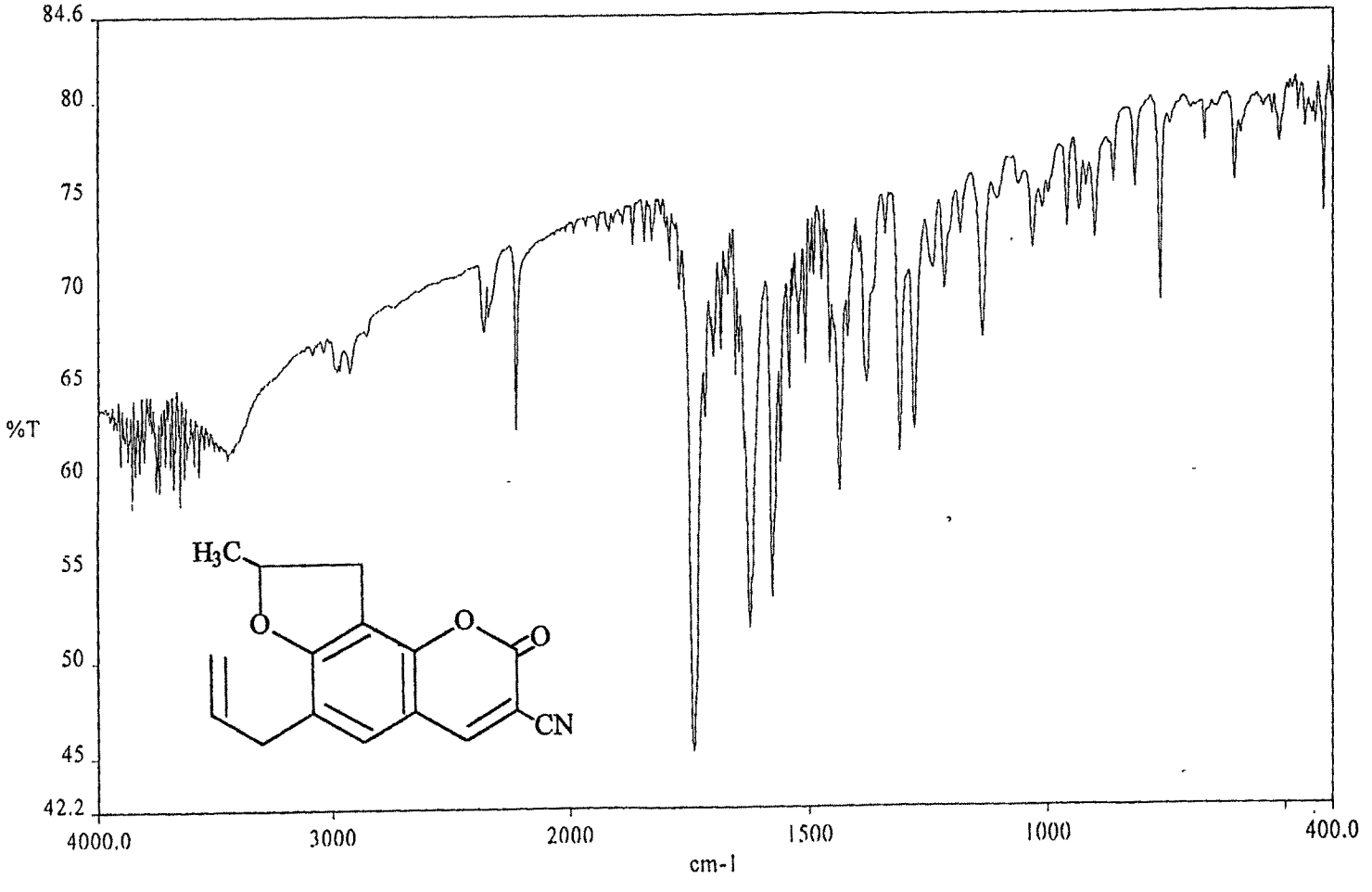


Fig. II.22

cyano-2-methyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one (132). The IR bands appeared at 2228 and 1742cm^{-1} are accounted for -CN and >CO of lactone **[Fig. II.23]** and the PMR in $CDCl_3$ at δ 1.55 as doublet for three methyl protons at C-2; a multiplet at 3.30 for two protons at C-3; another doublet at 3.40 for two -CH_2- of allyl chain -$C\underline{H}_2$-CH=CH_2 at C-9; a multiplet at 5.15 for two terminal protons of -CH_2-CH=$C\underline{H}_2$ at C-9 overlapped with proton at C-2; another multiplet at 6.00 for proton of -CH_2-$C\underline{H}$=CH_2 at C-9 and two singlets appeared at 7.15 and 8.05 for protons at C-8 and C-7 respectively. **[Fig. II.24]**

The structure of the product was further confirmed by the ortho migration of allyl group as reported by Cairns *et al.*[75] during the Claisen rearrangement of 2-allyloxy-4-alkoxycinnamates to 8-allylcoumarin and related compounds from position C-2 to C-3. It could be attributed from the Claisen rearrangement that **130** has undergone two simultaneous transformations to yield **131**: In the first step ortho migration of both the allyl groups from C-2 to C-3 and C-4 to C-5 take place, which is followed in the second step by the formation of pyrone ring, eliminating ethanol molecule and angular dihydrofuran ring due to regiospecificity.

The structure was also confirmed by subjecting a similar Claisen rearrangement of ethyl-2-allyloxy-4-benzyloxy-α-carboethoxycinnamate (136) in DMA, furnished an 8-allylcoumarin derivative **137**. **[Scheme II.33]** Its PMR spectrum in $CDCl_3$ showed signals at δ 1.45, a triplet for three methyl group protons in ester at C-3; a doublet at 3.70 for two methylene protons of -$C\underline{H}_2$-CH=CH_2 at C-8; a quartet at 4.40 for two methylene protons of -CH_2- in ester at C-3; a multiplet at 4.95-5.20 for two methylene protons of -CH_2-CH=$C\underline{H}_2$ at C-8; a singlet at 5.25 two methylene protons of -$C\underline{H}_2C_6H_5$ at C-7; a multiplet at 5.75-6.15 for proton of -CH_2-$C\underline{H}$=CH_2 at C-8; a doublet at 6.95 for proton at C-6; a multiplet at 7.30-7.55 for five protons of -$CH_2C_6\underline{H}_5$ at C-7 and proton at C-5 and a singlet at 8.40 for proton at C-4 **[Fig. II.25]**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cm-1
H3C
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O
O
CN

Fig. II.23

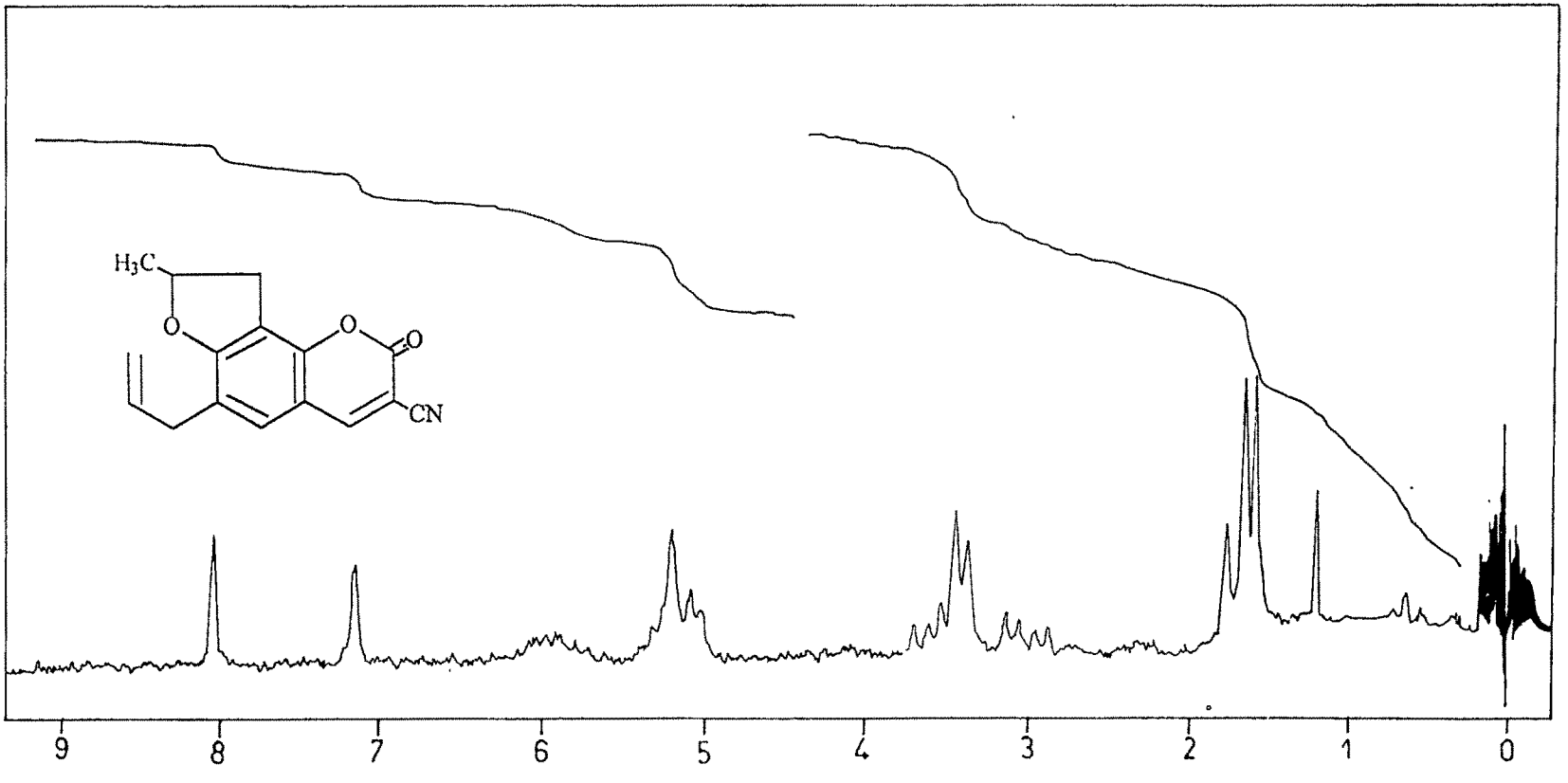
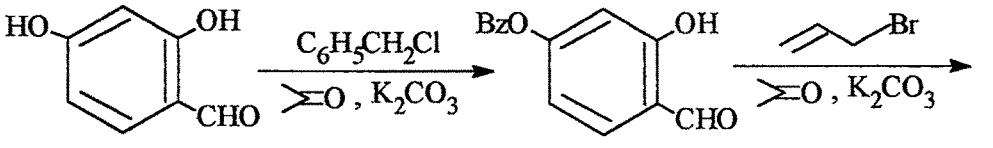
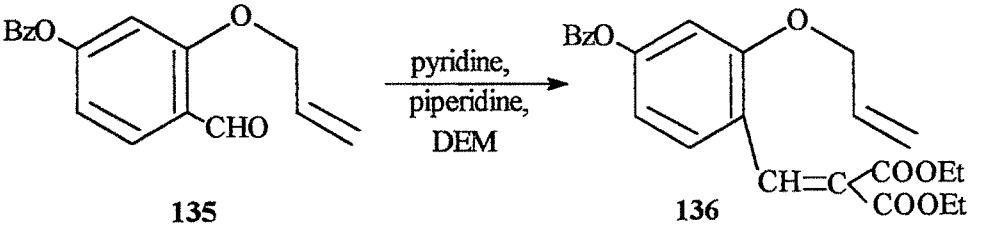


Fig. II.24

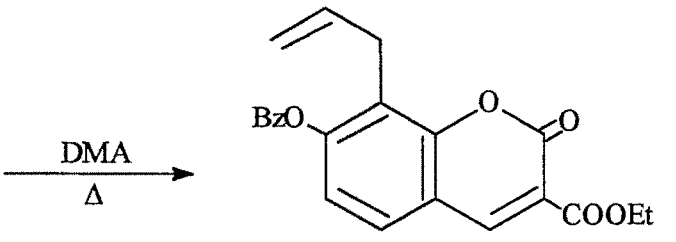
Scheme II.33



134



135 136



137

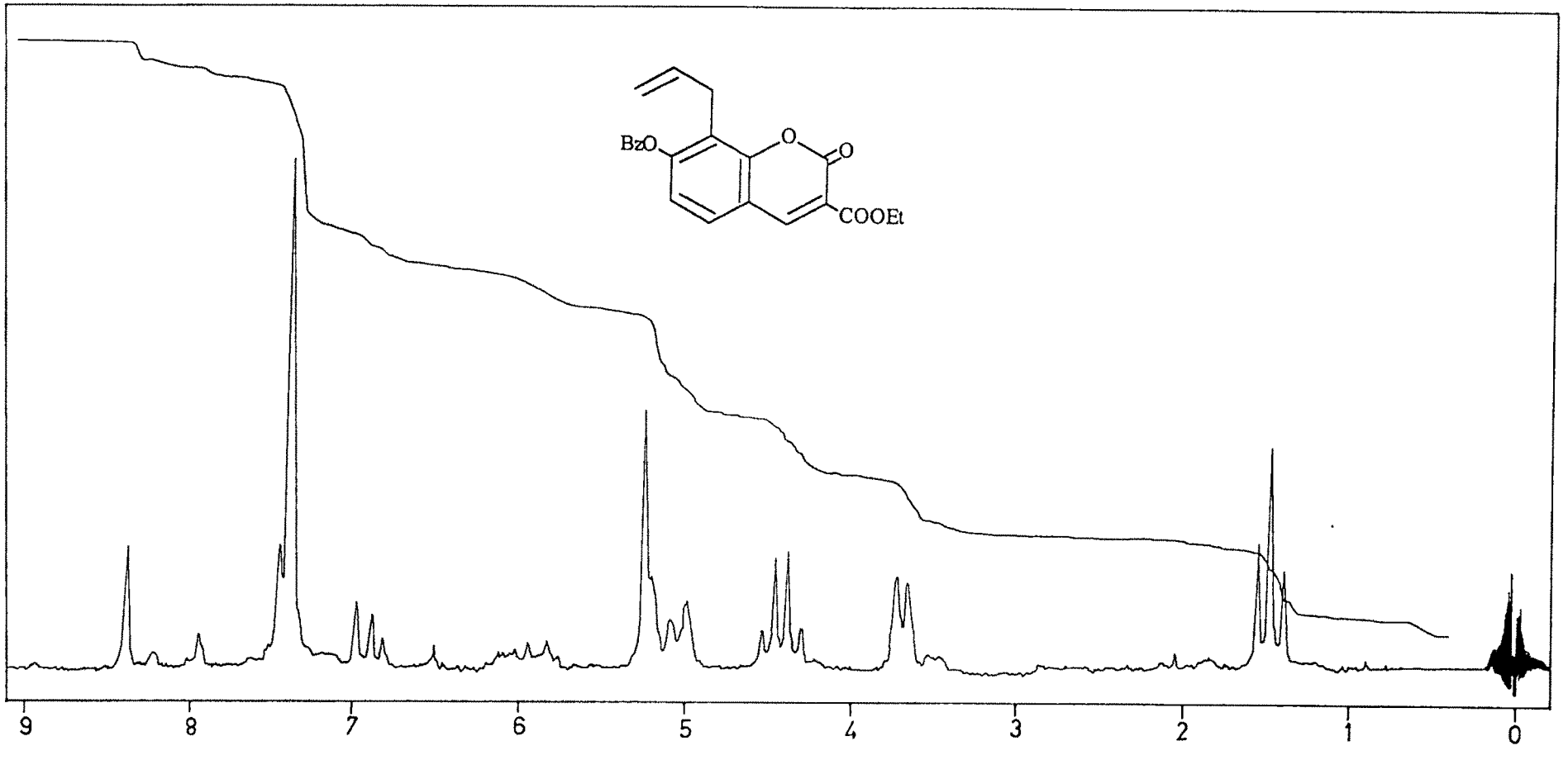


Fig. II.25

indicates beyond doubt that the allyl group migrates to the ortho position in such systems rather than to para position.

132 was then subjected to dehydrogenation with Pd/C (10%) in diphenylether gave an unusual and unexpected product 9-(1′-propenyl)-6-cyano-2-methyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one (133), which exhibited IR bands in KBr at 2226 and 1737cm^{-1} due to -CN and >CO of lactone respectively **[Fig. II.26]** whereas the PMR signals in $CDCl_3$ and DMSO appeared as a doublet at δ 1.50 for three methyl group protons at C-2, another doublet at 1.85 for three methyl group protons of -CH=CH-C<u>H</u>$_3$ at C-9; a multiplet at 2.60-3.50 for two protons at C-3; a multiplet for a proton at C-2 appeared at 5.15; a broad singlet at 6.15 for two protons of -C<u>H</u>=C<u>H</u>-CH$_3$ at C-9; two singlets at 7.30 and 8.25 for protons at C-8 and C-7 respectively. **[Fig. II.27]**

The signals at δ 5.15 and 2.60-3.50 indicate that the dihydrofuran ring has not undergone dehydrogenation during the reaction. If it had taken place, the methyl group would have appeared as singlet and multiplet for protons at C-2 and C-3 would have disappeared. Secondly the pyrone ring is also intact from the downfield signal of a proton at C-4 and from IR spectrum for >C=O at 1737cm^{-1} and -CN at 2226cm^{-1} absorptions. It had shown only a change in allyl group signals, suggests some isomerization i.e. a shift of terminal double bond to the middle in the allyl group at C-9.

The above reaction was also attempted in refluxing diphenylether alone in the absence of Pd/C to observe the possible isomerization, gave only the starting compound. No dehydrogenation was observed with DDQ in dry benzene.

A facile synthesis of ethyl-9-allyl-6-carboethoxy-2-methyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one (140) was also carried out from liquid mixture of **128** and **129**, which was taken as such for condensation with diethylmalonate, on usual work up afforded a mixture of open chain product ethyl-2,4-diallyloxy-α-carboethoxycinnamate (138) and ethyl-7-allyloxy

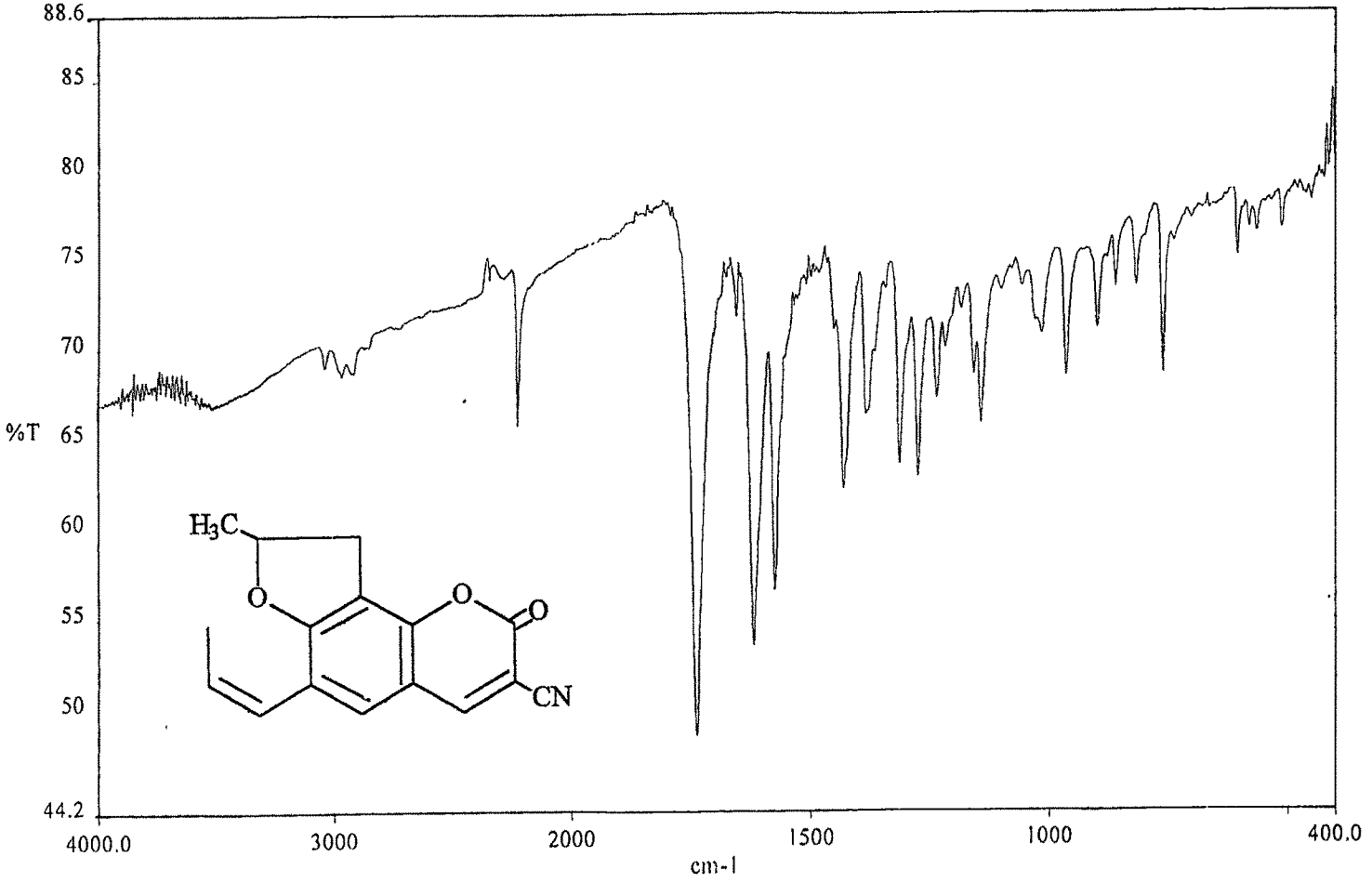

88.6
85
80
75
70
%T 65
60
55
50
44.2
4000.0
3000
2000
1500
1000
400.0
cm-1
H3C
O
O
O
CN

Fig. II.26

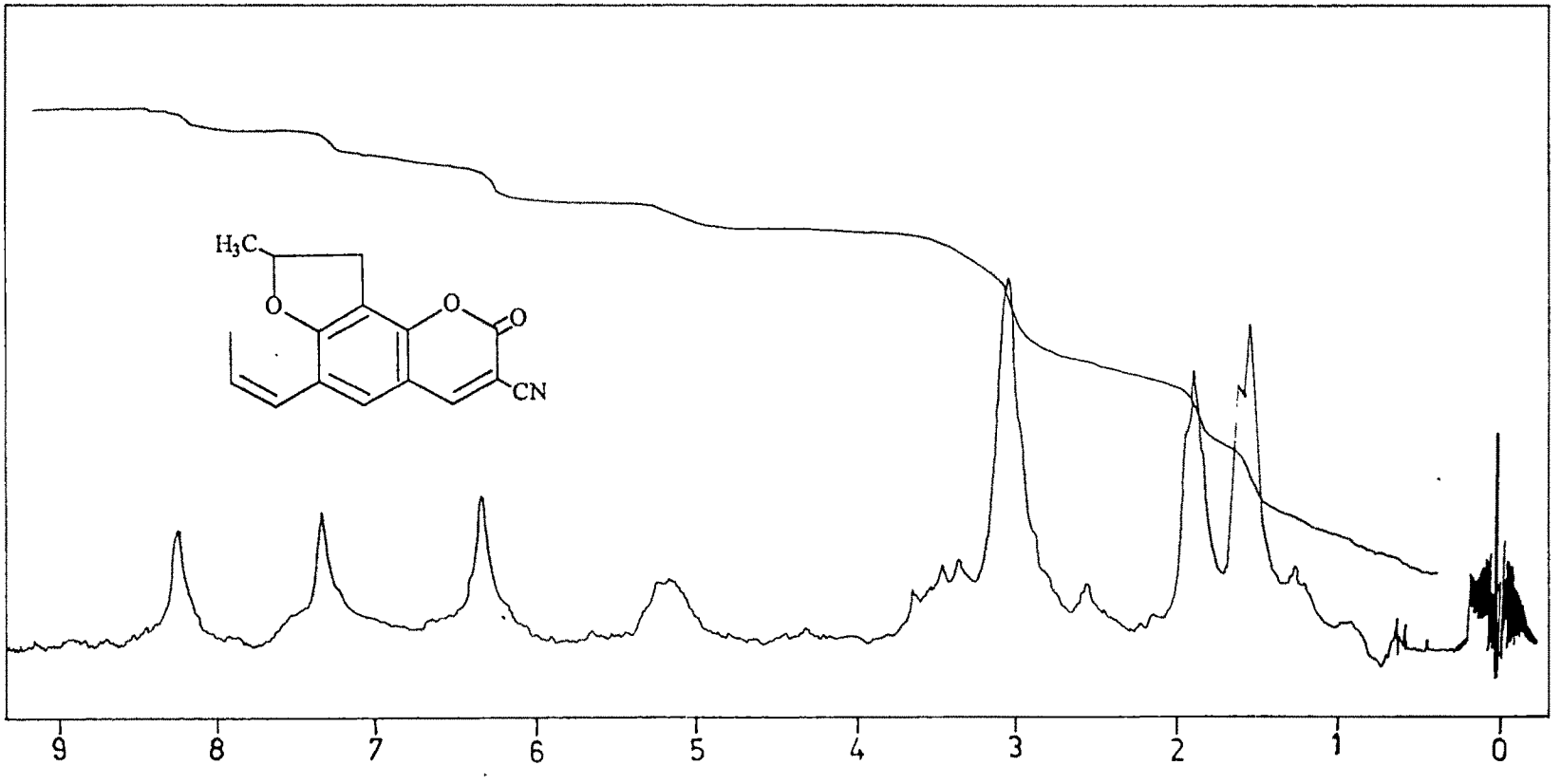
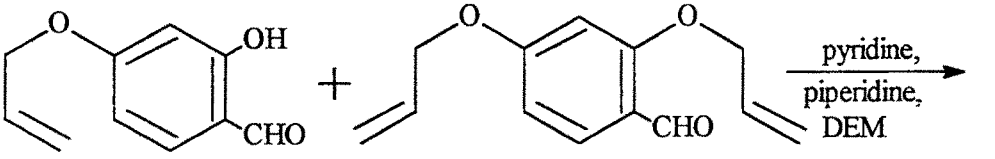


Fig. II.27

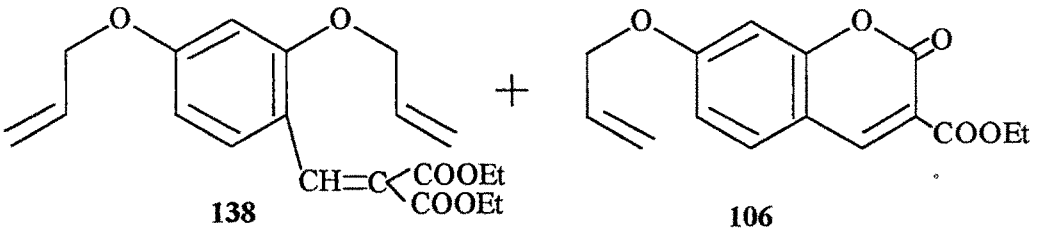
benzopyran-2H-one-3-carboxylate (106). Both the products were separated by column chromatography. The structure of **138** was assigned from the elemental analysis and PMR spectrum, whereas the formation of other product **106** was confirmed by comparison with compound **106** which was obtained by Knoevenagel condensation as shown in Scheme II.25, on the basis of elemental analysis and mmp. **[Scheme II.34]** **138** on Claisen rearrangement resulted in the formation of ethyl-9-allyl-2-methyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one-6-carboxylate (139), which was confirmed by elemental analysis, PMR and CMR spectra. Its PMR spectrum showed signals in $CDCl_3$ as δ 1.50, a triplet for three methyl group protons of ester at C-6; a doublet at 1.65 for three methyl group protons at C-2; a multiplet at 2.90-3.80 for two methylene protons at C-3; a doublet at 3.45 for two methylene protons of $-C\underline{H}_2-CH=CH_2$ at C-9; a quartet at 4.45 for two methylene protons of ester at C-6; two multiplets at 5.10-5.35 and 5.80-6.20 for two protons of $-CH_2-CH=C\underline{H}_2$ overlapped with proton at C-2 and a proton of $-CH_2-C\underline{H}=CH_2$ at C-9 respectively and two singlets at 7.25 and 8.45 for protons at C-8 and C-7 **[Fig. II.28]** and CMR exhibited signals in $CDCl_3$ as δ 14.30 (CH_3 of ester at C-6); 21.95 (CH_3 at C-2); 33.14 (CH_2 at C-3); 33.86 (CH_2 of allyl group at C-9); 61.51 (CH_2 of ester at C-6); 82.54 ($=CH_2$ of allyl group at C-9); 112.14; 112.76; 116.79 (CH at C-2); 120.65; 130.36 (CH of allyl at C-9); 135.07 (CH at C-8); 149.10; 149.53 (CH at C-7); 151.83 (C-3a); 157.34 (C-7a); 163.65 (>CO of lactone at C-2); 164.53 (>CO of ester at C-6). **[Fig. II.29]**

Dehydrogenation of **139** was attempted with Pd/C in diphenylether at refluxing temperature gave the same type of isomeric product ethyl-9-(1′-propenyl)-2-methyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one-6-carboxylate (140) as in the case of cyano derivative. The structure of the product was deduced from elemental analysis, PMR, CMR and X-ray crystallographic studies. Its PMR in $CDCl_3$ showed signals at δ 1.50, a triplet for $-CH_3$ of ester at C-6; a doublet at 1.65 for $-CH_3$ at C-2; a doublet at 1.90 for $-CH_3$ of $-CH=CH-C\underline{H}_3$ at C-9; a multiplet at 2.70-3.80 for 2H at C-3; a

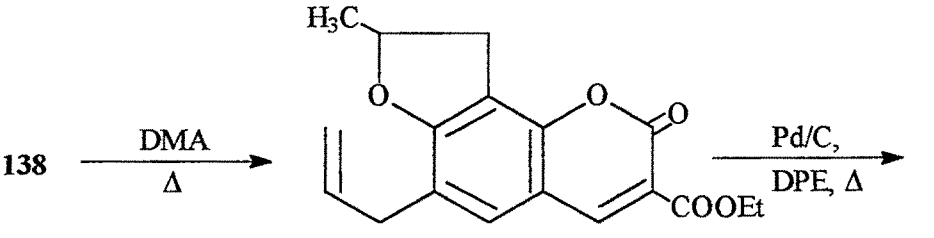
Scheme II.34



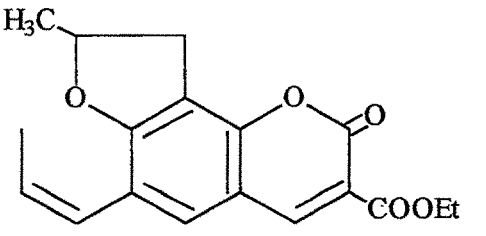
128 **129**



138 **106**



139



140

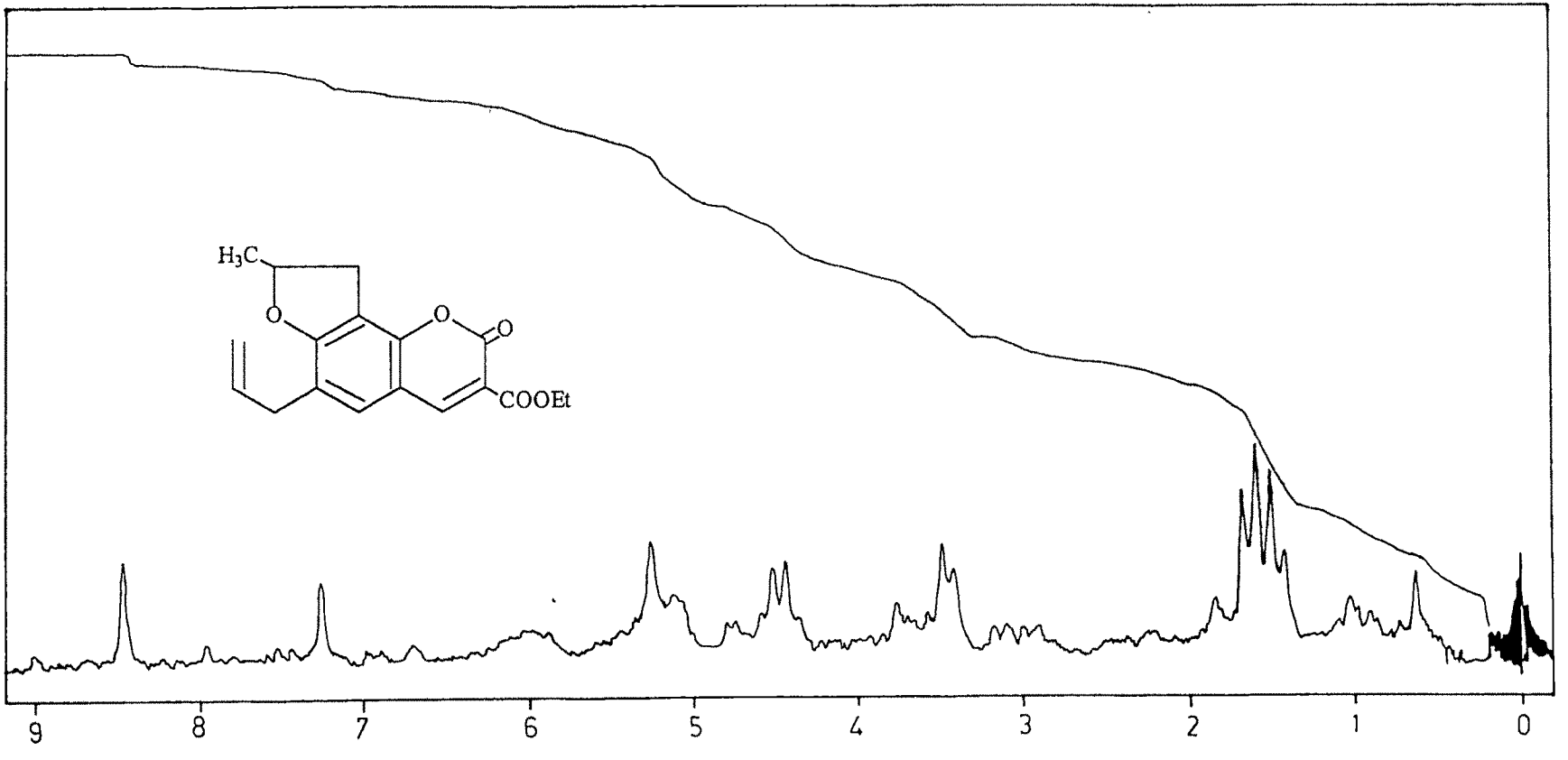


Fig. II.28

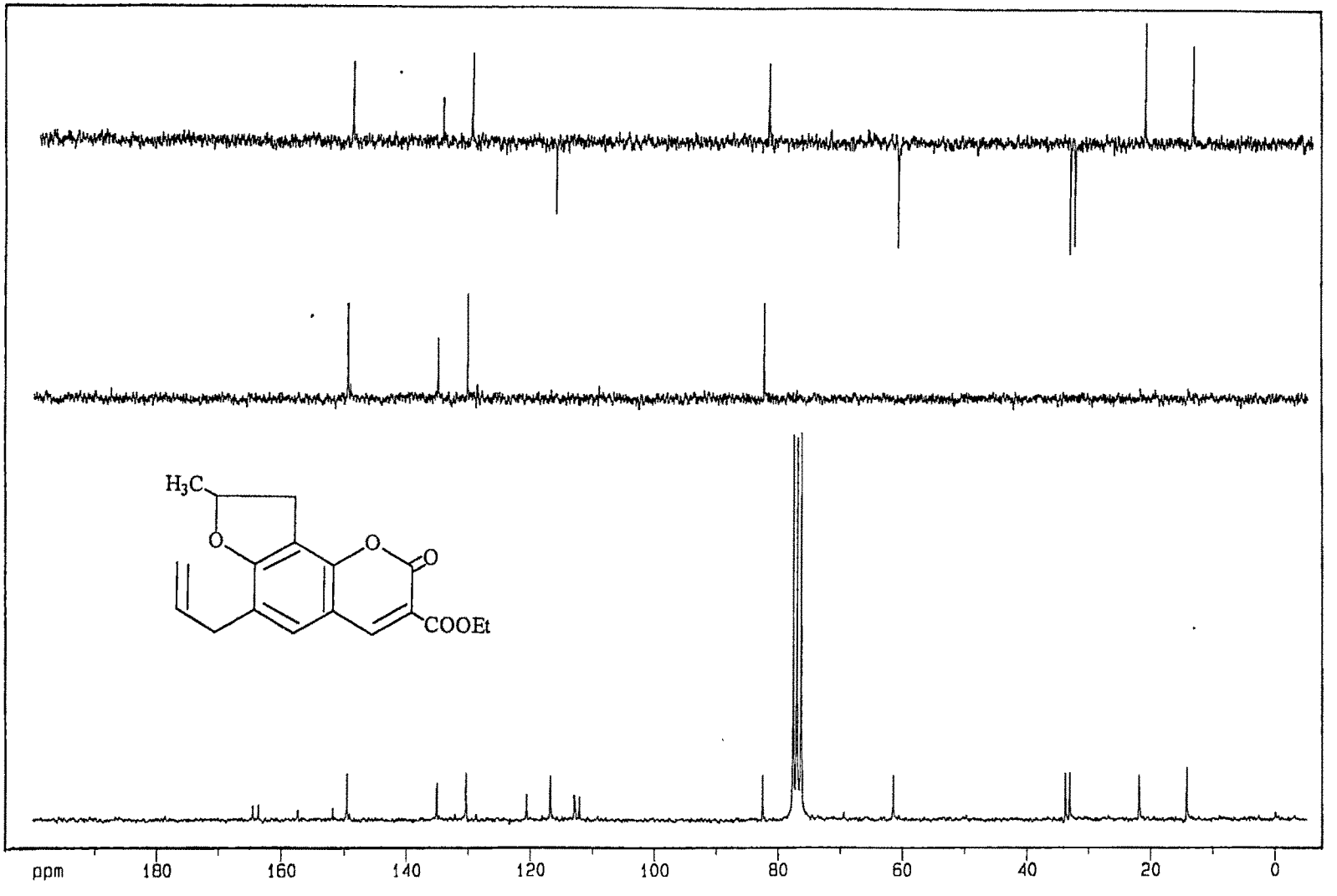


Fig. II.29

quartet at 4.45 for -CH_2- of ester at C-6; a multiplet at 5.20 for proton at C-2; a broad singlet at 6.40 for two protons of -C<u>H</u>=C<u>H</u>-CH_3 at C-9 and two singlets at 7.30 and 8.40 for protons at C-8 and C-7. **[Fig. II.30]** and CMR in $CDCl_3$ exhibited signals at δ 14.30 (CH_3 of ester at C-6); 18.97 (CH_3 at C-2); 21.99 (CH_3 of propenyl group at C-9); 33.52 (CH_2 at C-3); 61.56 (CH_2 of ester at C-6); 82.75 (CH at C-2); 112.26; 113.20; 113.56; 119.73; 124.28 (=CH of propenyl group at C-9); 127.76 (CH of propenyl group at C-9); 129.33 (CH at C-8); 149.47 (CH at C-7); 151.46 (C-3a); 157.17 (C-7a); 163.39 (>CO of lactone at C-5); 163.62 (>CO of ester at C-6). **[Fig. II.31]**

The general view of the molecule from the X-ray crystallographic studies indicating the atom numbering scheme and the molecular packing in the unit cell down a-axis are shown in **[Fig. II.32 & II.33]** Unit cell parameters and basic information about data collection and structure refinement are summarized in experimental section.

In a similar way a mixture of **128** and **129** was condensed directly with ethylacetoacetate to give a liquid product, which appeared to be a mixture of three products by TLC. The products having closer R_f values eluted out from petroleum ether, could not be further separated either by column chromatography. or TLC. The elemental analysis of this unseparable liquid and its PMR spectrum confirmed it as a mixture of E- and Z- ethyl-2,4-diallyloxy-α-acetylcinnamate (141a, 141b). **[Scheme II.35]** Its PMR signals in $CDCl_3$ showed two triplets at δ 1.26 for three protons of -CH_3 of E, Z isomers in the ester linkage; two singlets at 2.25 and 2.35 for -CH_3 of acetyl group corresponds to E, Z isomers; two quartets at 4.25 (overlapped) of -CH_2- groups corresponds to E, Z isomers in the ester linkage; a multiplet at 4.55 for four protons of 2x -CH_2- of -O<u>CH_2</u>CH=CH_2 at C-2 and C-4; a multiplet at 5.50 for four protons of 2x -CH_2- of -OCH_2CH=C<u>H_2</u> at C-2 and C-4; a multiplet at 6.10 for two protons of 2x -CH- of -OCH_2C<u>H</u>=CH_2 at C-2 and C-4; another multiplet

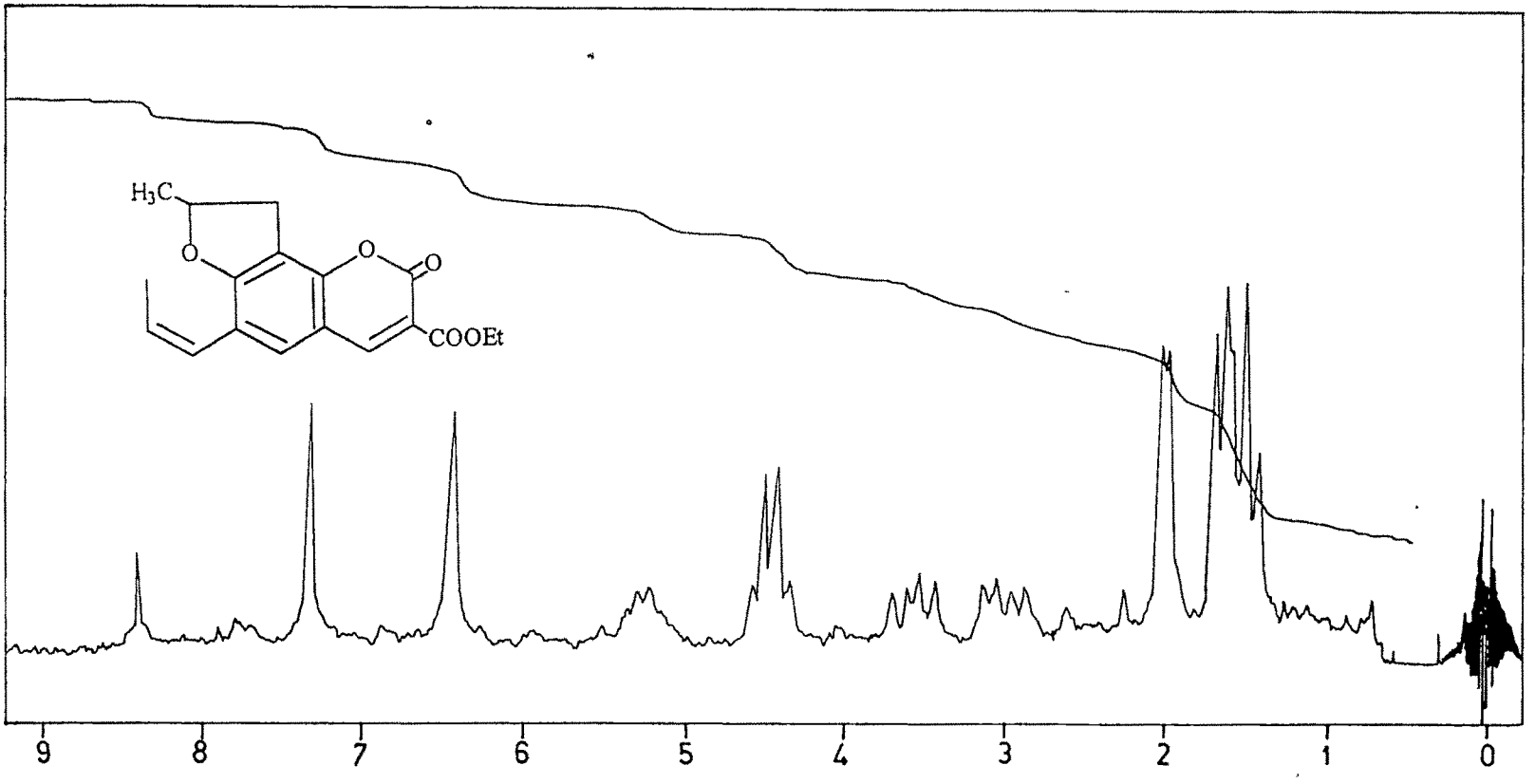


Fig. II.30

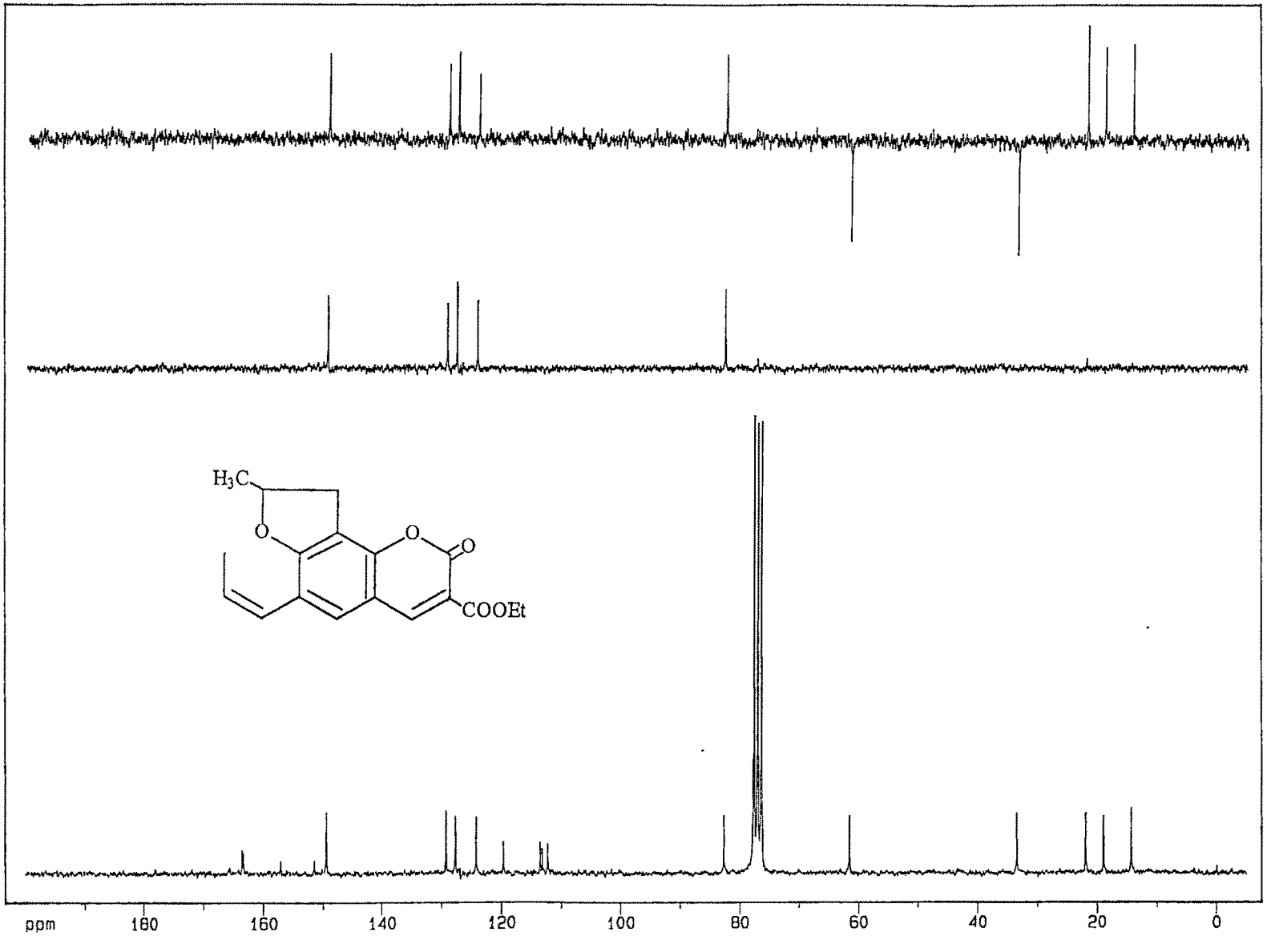


Fig. II.31

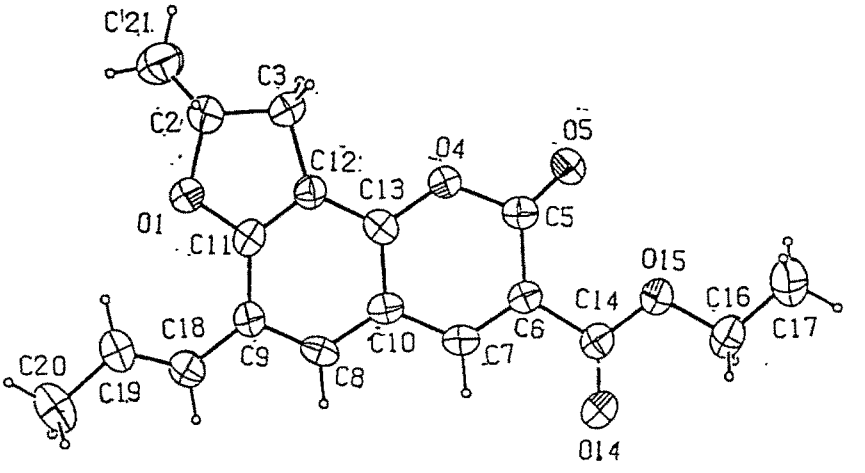

C21
C3
C2
C12
O4
O5
O1
C11
C13
C5
O15
C14
C16
C17
C18
C9
C10
C6
C7
C20
C19
C8
O14

Fig. II.32

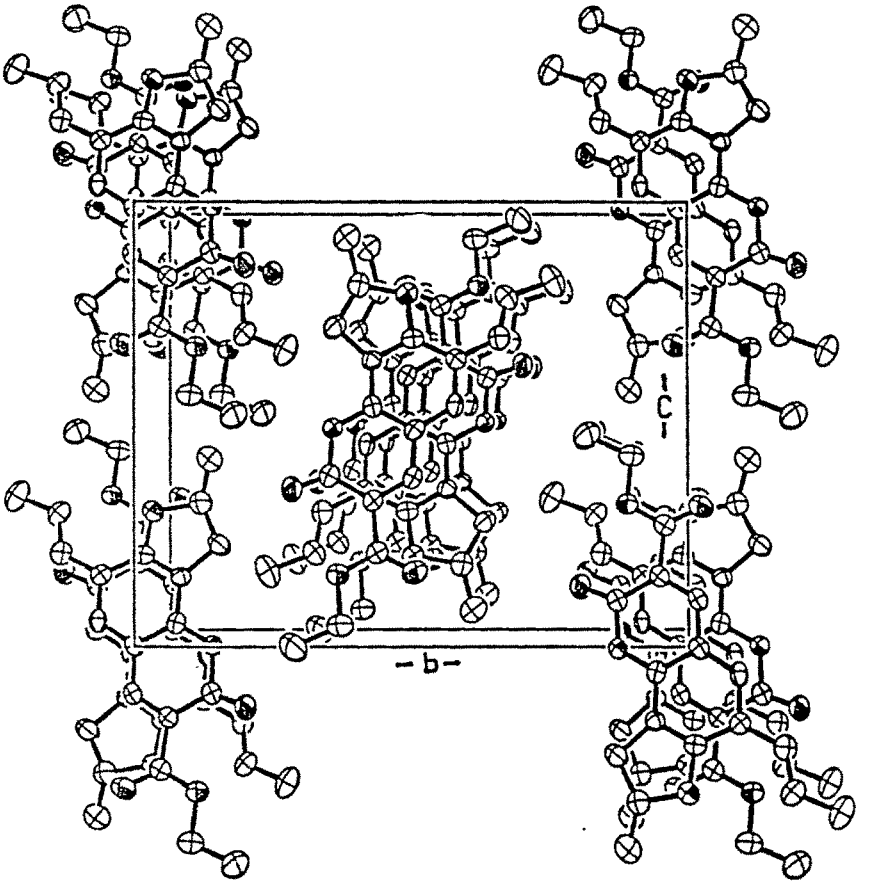
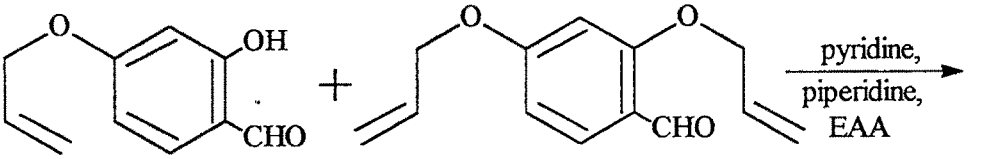
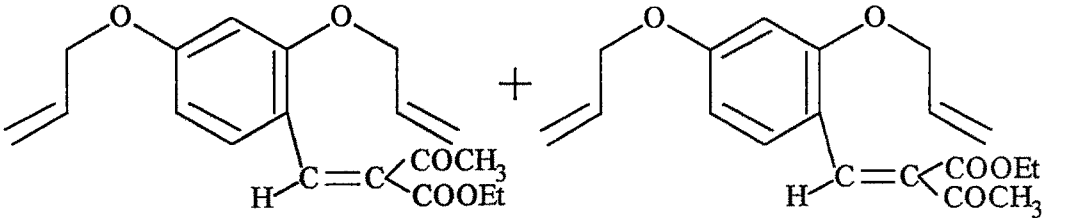


Fig. II.33

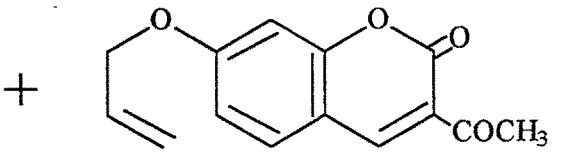
Scheme II.35



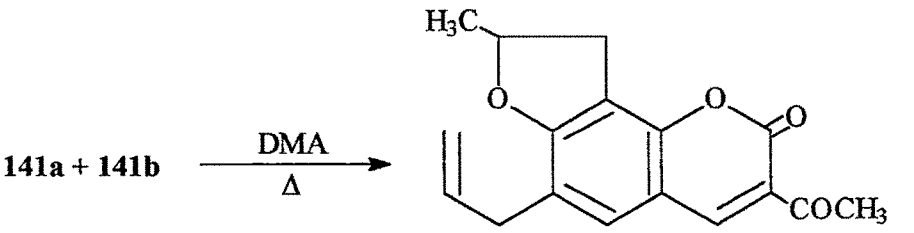
128 **129**



141a **141b**



117



142

at 6.50 for two protons at C-3 and C-5; two singlets at 7.95 and 8.00 for a proton of -CH=C< at C-1 corresponds to two isomers at β-carbon in the cinnamyl chain respectively. **[Fig. II.34]** The PMR spectrum of the isomeric mixture clearly showed the signals of each isomer. The proton integration of each isomer was observed to show in the ratio of 35 and 65.

The third product was isolated by column chromatography in 50:50 mixture of petroleum ether and benzene and its structure was confirmed by elemental analysis, TLC comparison and mmp with **117**, which was obtained by Knoevenagel condensation. **141a, 141b** was refluxed with N,N-DMA resulted in the formation of 9-allyl-6-acetyl-2-methyl-2,3-dihydrofuro(2,3-h) benzopyran-5H-one (142) in very poor yield.

It was noticed, during the condensations with the three active methylene compounds, that in the first condensation with ethylcyanoacetate, it yielded only one isomer and as discussed earlier it could most probably an E-isomer. In the condensation of diethylmalonate it only afforded single product due to the absence of other geometric possibility, while in the condensation with ethylacetoacetate it accounted two isomers E and Z.

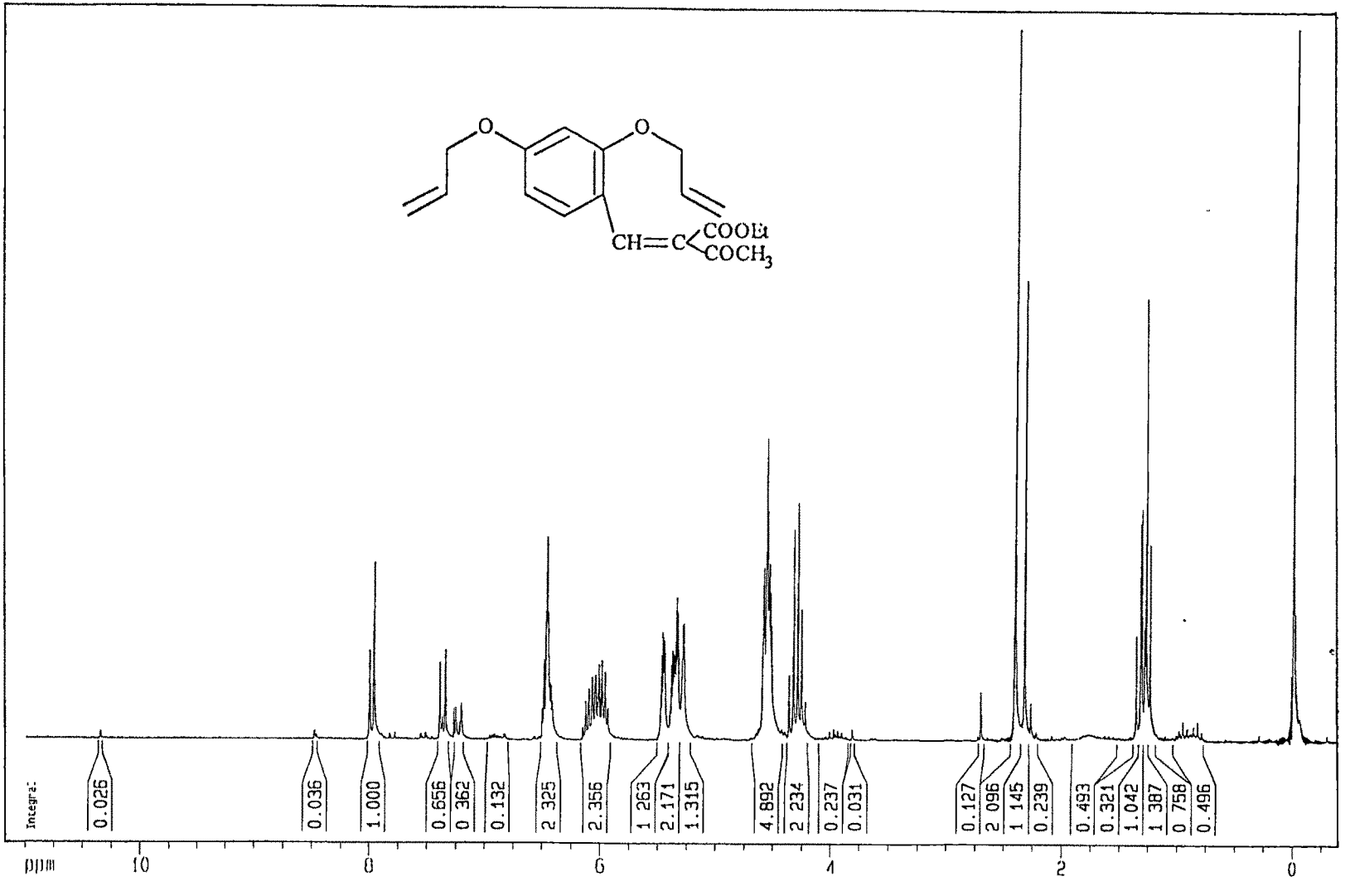

O
O
CH=C
COOEt
COCH3
Integral
0.026
0.036
1.000
0.656
0.362
0.132
2.325
2.356
1.263
2.171
1.315
4.892
2.234
0.237
0.031
0.127
2.096
1.145
0.239
0.493
0.321
1.042
1.387
0.758
0.496
ppm
10
8
6
4
2
0

Fig. II.34

EXPERIMENTAL

Melting points were determined by open capillary method and are uncorrected. Elemental analysis was carried out on Colemen instrument. Infrared spectra were recorded on Perkin-Elmer FT-IR spectrometer (Spectrum RX 1). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker 200MHz or Perkin-Elmer 90MHz spectrophotometer. An Enraf Nonius CAD-4 single crystal X-ray diffractometer was used for the X-ray crystallographic studies.

Ethyl-7-hydroxybenzopyran-2H-one-3-carboxylate (105):

An equimolar amount of 2,4-dihydroxybenzaldehyde (10g, 72.4mmol) and diethylmalonate (11.6ml, 72.4mmol) was dissolved in dry pyridine (10ml) using piperidine (0.5ml, 6.0mmol) as a base. The reaction mixture was left at 50-60°C for 24h and then dropped into ice-HCl. Separated product was filtered and recrystallized from ethanol as yellow needles (13.1g; 77.5%), m.p. 172°C.

Analysis : Found : C, 61.91%; H, 4.14%

$C_{12}H_{10}O_5$: Requires : C, 61.53%; H, 4.27%

Ethyl-7-allyloxybenzopyran-2H-one-3-carboxylate (106):

A solution of ethyl-7-hydroxybenzopyran-2H-one-3-carboxylate (10g, 42.7mmol) in dry DMF (40ml) was heated with potassium carbonate (15g, 0.11mole) and allylbromide (5.2ml, 42.7mmol) on a steambath for 6.5h. The reaction was worked up and the obtained product was treated with dilute alkali to remove unreacted starting material. The product recrystallized from benzene and petroleum ether mixture (80:20) as pale yellow needles (9.4g; 80.3%), m.p. 109-110°C.

Analysis : Found : C, 65.45%; H, 5.52%

$C_{15}H_{14}O_5$: Requires : C, 65.69%; H, 5.11%

IR(KBr) cm^{-1} : 3074, 2989, 2945, 1761, 1620, 1384, 1277, 1213

Ethyl-7-hydroxy-8-allylbenzopyran-2H-one-3-carboxylate (107):

Ethyl-7-allyloxybenzopyran-2H-one-3-carboxylate (2g, 7.3mmol) was refluxed with N,N-dimethylaniline (14ml) for 7.5h. The reaction mixture was then poured into ice cold HCl and product thus obtained was stirred with mild alkali for 15min. to separate alkali soluble and insoluble fractions.

The alkali soluble fraction was acidified with dilute HCl. Separated product filtered, dried and checked on TLC as a single spot. The product was recrystallized from ethanol (0.2g; 10.0%), m.p. 211-2°C.

Analysis : Found : C, 65.96%; H, 5.20%

$C_{15}H_{14}O_5$: Requires : C, 65.69%; H, 5.11%

IR(KBr) cm^{-1} : 3272, 3072, 2982, 2950, 1750, 1710, 1602, 1569, 1233

Ethyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one-6-carboxylate (108):

The alkali insoluble fraction was purified by passing through column chromatography using mixture of petroleum ether and benzene (50:50), which showed single spot on TLC and finally recrystallized from benzene and petroleum ether mixture (80:20) (0.8g; 40.0%), m.p. 160°C.

Analysis : Found : C, 65.47%; H, 5.39%

$C_{15}H_{14}O_5$: Requires : C, 65.69%; H, 5.11%

IR(KBr) cm^{-1} : 3080, 2995, 2947, 1756, 1607, 1251

Ethyl-2-methylfuro(2,3-h)benzopyran-5H-one-6-carboxylate (109):

Ethyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one-6-carboxylate (2.10g, 7.7mmol) in distilled carbontetrachloride (100ml) was added to freshly prepared N-bromosuccinimide (1.35g, 7.7mmol) and a pinch of benzoyl peroxide, an initiator. The reaction mixture was refluxed for 16h under irradiation with 200W-tungsten lamp, which was then filtered hot to remove separated succinimide during the reaction. Excess of CCl_4 was distilled off to give a solid, which appeared to be a mixture of two products with close difference in R_f value on TLC. As they could not be separated by column

chromatography, these products were subjected to fractional crystallization using ethanol as solvent. The product separated first from ethanol was crystallized repeatedly till it show single spot on TLC was assigned as **109** (0.7g; 33.6%), m.p. 143°C.

Analysis : Found : C, 65.93%; H, 4.36%

$C_{15}H_{12}O_5$: Requires : C, 66.17%; H, 4.41%

IR(KBr) cm^{-1}: 3075, 2979, 2950, 1756, 1699, 1602, 1261

Ethyl-2-bromomethylfuro(2,3-h)benzopyran-5H-one-6-carboxylate (110):

The mother liquor was concentrated, which on repeated crystallization with ethanol gave yellow floppy needles (0.7g; 26.0%), m.p. 220°C.

Analysis : Found : C, 51.37%; H, 3.51%

$C_{15}H_{11}O_5Br$: Requires : C, 51.28%; H, 3.13%

IR(KBr) cm^{-1}: 3078, 2985, 2950, 1740, 1699, 1610, 1508, 1250

2-Piperidinomethyl-6-piperidinocarbonylfuro(2,3-h)benzopyran-5H-one (111):

Ethyl-2-bromomethylfuro(2,3-h)benzopyran-5H-one-6-carboxylate (0.3g, 0.8mmol) in N,N-dimethylformamide (8ml) and piperidine (0.3ml, 3.6mmol) was refluxed for 55min.. The reaction mixture was cooled and poured into ice water. Separated product was purified by column chromatography using chloroform and methanol mixture (2.5%) as an eluent. The product crystallized from ethanol as pale pink crystals (0.25g; 73.5%), m.p. 209°C.

Analysis : Found : C, 69.97%; H, 6.43%; N, 6.88%

$C_{23}H_{26}O_4N_2$: Requires : C, 70.05%; H, 6.60%; N, 7.11%

Ethyl-7-hydroxy-8-(2′,3′-dibromopropyl)benzopyran-2H-one-3-carboxylate (112):

Ethyl-7-hydroxy-8-allylbenzopyran-2H-one-3-carboxylate (1.4g, 5.1mmol) was dissolved in acetic acid (25ml) and Br_2 in acetic acid (0.8g,

5.1mmol) was added dropwise by addition funnel with constant stirring. After the completion of addition stirring was continued for 1h and then left the reaction contents overnight at room temperature. It was poured in cold water to give a solid, which was recrystallized from ethanol as pink amorphous product (2g; 90.5%), m.p. 232°C.

Analysis	:	Found	:	C, 41.81%; H, 3.61%
$C_{15}H_{14}O_5Br_2$	:	Requires	:	C, 41.47%; H, 3.22%

Ethyl-2-bromomethyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one-6-carboxylate (113):

Ethyl-7-hydroxy-8-(2′,3′-dibromopropyl)benzopyran-2H-one-3-carboxylate (0.7g, 1.6mmol) in dry benzene (70ml) and triethylamine (0.2ml, 2.0mmol) was stirred for 24h at room temperature. Excess of benzene was distilled and the product was then treated with dilute HCl to remove traces of triethylamine. It was then treated with dilute alkali to remove unreacted starting material. The resulting product was recrystallized from ethanol to give colourless needles (0.4g; 70.2%), m.p. 165°C.

Analysis	:	Found	:	C, 51.37%; H, 3.91%
$C_{15}H_{13}O_5Br$	:	Requires	:	C, 50.99%; H, 3.68%

Ethyl-7-hydroxy-8-iodobenzopyran-2H-one-3-carboxylate (114):

(A) *Iodination with iodic acid:*

Ethyl-7-hydroxybenzopyran-2H-one-3-carboxylate (2.2g, 9.4mmol) in ethanol (40ml) was stirred by adding a mixture of iodic acid (0.3g, 1.8mmol) and iodine (0.9g, 3.5mmol) in ethanol (10ml), taken in a dropping funnel. Stirring was continued for one more hour after the completion of the addition. The crude product separated out during the reaction was filtered and recrystallized from ethanol to give **114** as yellow amorphous powder (2.9g; 85.3%), m.p. 265°C.

Analysis : Found : C, 40.38%; H, 2.92%

$C_{12}H_9O_5I$: Requires : C, 40.00%; H, 2.50%

(B) *Iodination with ammonia:*

Ethyl-7-hydroxybenzopyran-2H-one-3-carboxylate (2.3g, 9.8mmol) was dissolved in liquor ammonia (13ml) and water (40ml). The iodinating solution-iodine (2.9g, 11.4mmol) and KI (5.8g, 34.9mmol) dissolved in H_2O (10ml) was added dropwise from a dropping funnel with constant stirring and continued stirring for further 30min. After the completion of addition, mixture was poured into chilled dilute H_2SO_4 (13-15ml conc. H_2SO_4 in 100-150ml H_2O). Separated solid recrystallized from excess of ethanol to give the product as yellow amorphous solid (2.7g; 77.1%), m.p. 264°C.

Analysis : Found : C, 39.79%; H, 2.93%

$C_{12}H_9O_5I$: Requires : C, 40.00%; H, 2.50%

Ethyl-7-allyloxy-8-iodobenzopyran-2H-one-3-carboxylate (115):

Ethyl-7-hydroxy-8-iodobenzopyran-2H-one-3-carboxylate (5g, 13.9mmol) in dry DMF (40ml) with freshly fused K_2CO_3 (10g, 72.4mmol) and allylbromide (1.7ml, 13.9mmol) was heated at 100°C for 6h. The completion of the reaction was checked with dilute NaOH and reaction mixture was poured over crushed ice. The resulting solid was filtered and treated with dilute alkali to remove unreacted starting material. Recrystallization from a mixture of benzene and petroleum ether (50:50) afforded the product as pale yellow needles (4.2g; 76.3%), m.p. 192°C.

Analysis : Found : C, 45.32%; H, 3.17%

$C_{15}H_{13}O_5I$: Requires : C, 45.00%; H, 3.25%

IR(KBr) cm^{-1} : 3075, 2980, 2955, 1752, 1690, 1603, 1530, 1218

Attempted Claisen rearrangement of ethyl-7-allyloxy-8-iodobenzopyran-2H-one-3-carboxylate:

Ethyl-7-allyloxy-8-iodobenzopyran-2H-one-3-carboxylate (2g, 5mmol) was refluxed with N,N-DMA (14ml) for 6.5h. The reaction mixture was then poured into ice containing HCl and separated solid was treated with dilute alkali to separate alkali soluble and insoluble fractions.

Alkali soluble fraction was acidified with dilute HCl, separated product was filtered and recrystallized from ethanol as colourless needles (0.25g; 18.2%), m.p. 211-12°C.

Analysis : Found : C, 65.28%; H, 5.49%

$C_{15}H_{14}O_5$: Requires : C, 65.69%; H, 5.11%

Alkali insoluble fraction was purified by column chromatography using petroleum ether and benzene mixture (50:50), which showed single spot on TLC and recrystallized from benzene and petroleum ether (80:20) to give the product as yellow solid (0.4g; 29.1%), m.p. 160°C.

Analysis : Found : C, 65.99%; H, 5.07%

$C_{15}H_{14}O_5$: Requires : C, 65.69%; H, 5.11%

7-Hydroxy-3-acetylbenzopyran-2H-one (116):

A mixture of 2,4-dihydroxybenzaldehyde (10g, 72.4mmol) in dry pyridine (10ml), piperidine (0.5ml, 5.9mmol) and ethylacetoacetate (9.4ml, 72.4mmol) was left at 50-60°C for 24h. The contents were poured into cold dilute HCl and separated solid was recrystallized from ethanol to give **116** as pale green needles (10.5g; 70.9%), m.p. 236°C.

Analysis : Found : C, 65.12%; H, 3.68%

$C_{11}H_8O_4$: Requires : C, 64.70%; H, 3.92%

7-Allyloxy-3-acetylbenzopyran-2H-one (117):

7-Hydroxy-3-acetylbenzopyran-2H-one (5g, 24.5mmol) in dry DMF (25ml) was heated with anhydrous K_2CO_3 (10g, 72.4mmol) and allylbromide

(3ml, 24.5mmol) at 100°C on steambath for 4h. The reaction mixture was then poured into ice cold water and separated product was treated with dilute alkali to remove unreacted starting material, which finally recrystallized from benzene as yellow needles (4.5g; 75%), m.p. 153°C.

Analysis : Found : C, 68.98%; H, 4.53%

$C_{14}H_{12}O_4$: Requires : C, 68.85%; H, 4.92%

IR(KBr) cm^{-1} : 3071, 2981, 2946, 1727, 1670, 1610, 1261, 1210

7-Hydroxy-8-allyl-3-acetylbenzopyran-2H-one (118):

7-Allyloxy-3-acetylbenzopyran-2H-one (2g, 8.2mmol) was refluxed with N,N-DMA (14ml) for 6h. The reaction mixture was then cooled and poured into cold dilute HCl. Separated solid was stirred with dilute alkali for 15min. to separate alkali soluble and insoluble fractions.

Alkali soluble fraction was acidified with dilute HCl and obtained product was recrystallized from ethanol as yellow cubes (0.5g, 25%), m.p. 200°C.

Analysis : Found : C, 68.49%; H, 4.73%

$C_{14}H_{12}O_4$: Requires : C, 68.85%; H, 4.92%

2-Methyl-6-acetyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one (119):

Alkali insoluble product was purified by column chromatography using benzene as eluent and recrystallized from ethanol to give **119** as yellow needles (0.8g, 40%), m.p. 201°C.

Analysis : Found : C, 69.13%; H, 5.23%

$C_{14}H_{12}O_4$: Requires : C, 68.85%; H, 4.92%

PMR($CDCl_3$): δ 1.50 (d, 3H of -CH_3 at C-2); 2.65 (s, 3H of -$COCH_3$ at C-6); 3.00 (m, 1H at C-3); 3.50 (m, 1H at C-3); 5.30 (m, 1H at C-2); 6.80 (d, J = 9Hz, 1H at C-9); 7.35(d, J = 9Hz, 1H at C-8); 8.40 (s, 1H at C-7)

2-Methyl-6-acetylfuro(2,3-h)benzopyran-5H-one (120):

A mixture of 2-methyl-6-acetyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one (2.2g, 9mmol) in distilled chloroform (100ml), N-bromosuccinimide (1.6g, 9mmol) and a pinch of benzoyl peroxide was refluxed under irradiation with tungsten-lamp (200W) for 16h. Separation of succinimide did not observe during the reaction. Excess of solvent was distilled and solid obtained after evaporation was heated with water to remove succinimide. Separated solid on TLC showed two distinct spots with minor difference in R_f value, appeared to be a mixture of two products, which were separated by fractional crystallization with ethanol.

The product, which separated first, on recrystallization with ethanol, yielded pale yellow needles (0.6g, 27.3%), m.p. 201°C.

Analysis : Found : C, 69.65%; H, 3.96%

$C_{14}H_{10}O_4$: Requires : C, 69.42%; H, 4.13%

PMR($CDCl_3$): δ 2.50 (s, 3H of $-CH_3$ at C-2); 2.70 (s, 3H, $-CH_3$ of $-COCH_3$ at C-6); 6.70 (s, 1H at C-3); 7.37(d, J = 7.5Hz for a proton at C-9); 7.44(d, J = 7.5Hz for a proton at C-8); 8.60 (s, 1H at C-7)

2-Bromomethyl-6-acetylfuro(2,3-h)benzopyran-5H-one (121):

The mother liquor was concentrated, which on repeated recrystallization with ethanol afforded yielded yellow needles (0.4g, 13.8%), m.p. 232°C.

Analysis : Found : C, 52.61%; H, 2.97%

$C_{14}H_9O_4Br$: Requires : C, 52.34%; H, 2.80%

7-Hydroxy-8-iodo-3-acetylbenzopyran-2H-one (122):

(A) *Iodination by iodic acid:*

To the 7-hydroxy-3-acetylbenzopyran-2H-one (3.5g, 17.2mmol) in ethanol (25ml), a mixture of iodic acid (0.6g, 3.4mmol) and iodine (1.7g, 6.7mmol) in ethanol (10ml) was added in small portions with stirring. The stirring was continued further 1h after the completion of addition. The crude

product separated out during the reaction was filtered and recrystallized from excess of ethanol to give **122** as yellow amorphous powder (4.2g; 73.7%), m.p. 290-1°C.

Analysis : Found : C, 39.81%; H, 1.84%

$C_{11}H_7O_4I$: Requires : C, 40.00%; H, 2.12%

(B) *Iodination by ammonia:*

7-hydroxy-3-acetylbenzopyran-2H-one (2.3g, 11.2mmol) was dissolved in liquor ammonia (13ml) and water (40ml). The iodinating solution- iodine (3.2g, 12.6mmol) and KI (6.4g, 38.5mmol) dissolved in H_2O (10ml) was added dropwise from a dropping funnel with stirring and continued stirring for further 30min. After the completion of addition, mixture was poured into chilled dilute H_2SO_4 (13-15ml conc. H_2SO_4 in 100-150ml H_2O). Separated solid on recrystallization with excess of ethanol afforded yellow amorphous product (2.5g; 67.5%), m.p. 291°C.

Analysis : Found : C, 39.68%; H, 1.75%

$C_{11}H_7O_4I$: Requires : C, 40.00%; H, 2.12%

7-Allyloxy-8-iodo-3-acetylbenzopyran-2H-one (123):

7-Hydroxy-8-iodo-3-acetylbenzopyran-2H-one (5g, 15.1mmol) in dry DMF (25ml), fused K_2CO_3 (10g, 72.4mmol) and allylbromide (1.9ml, 15.1mmol) were heated at on a steambath for 5h. The usual work up gave a solid, which on purification with column chromatography using petroleum ether and benzene mixture (50:50) followed by recrystallization from benzene gave pale yellow needles (3.8g; 67.8%), m.p. 188-9°C.

Analysis : Found : C, 45.03%; H, 2.67%

$C_{14}H_{11}O_4I$: Requires : C, 45.40%; H, 2.97%

PMR($CDCl_3$): δ 2.45 (s, 3H of $-CH_3$ of $-COCH_3$ at C-3); 4.75 (d, 2H of $-OC\underline{H}_2CH{=}CH_2$ at C-7); 5.25-5.65 (m, 2H of $-OCH_2CH{=}C\underline{H}_2$at C-7); 6.15 (m, 1H of $-OCH_2C\underline{H}{=}CH_2$ at C-7); 6.85 (d, J = 7Hz, 1H at C-6); 7.55 (d, J = 7Hz, 1H at C-5); 8.40 (s, 1H at C-4)

Attempted Claisen rearrangement of 7-allyloxy-8-iodo-3-acetylbenzopyran-2H-one:

7-Allyloxy-8-iodo-3-acetylbenzopyran-2H-one (2g, 5.4mmol) was refluxed with N,N-DMA (14ml) for 6h. The reaction mixture was then poured into ice containing HCl and separated solid was treated with dilute alkali to separate alkali soluble and insoluble fractions.

Alkali soluble fraction on acidification with dilute HCl, followed by recrystallization with ethanol gave product as yellow cubes (0.45g; 34.1%), m.p. 200°C.

Analysis : Found : C, 68.49%; H, 4.73%

$C_{14}H_{12}O_4$: Requires : C, 68.85%; H, 4.92%

Alkali insoluble fraction was purified by column chromatography using benzene and recrystallized from ethanol to give product as yellow needles (0.7g; 53.0%), m.p. 201°C.

Analysis : Found : C, 69.13%; H, 5.69%

$C_{14}H_{12}O_4$: Requires : C, 68.85%; H, 4.92%

Ethyl-7-hydroxy-8-methylbenzopyran-2H-one-3-carboxylate (124):

A solution of 2,4-dihydroxy-3-methylbenzaldehyde (5g, 33mmol) in dry pyridine (5ml), piperidine (0.2ml, 2.4mmol) and diethylmalonate (5.3ml, 33mmol) was left at 50-60°C for 24h. The reaction mixture on usual work up gave a solid, which was recrystallized from excess of ethanol as pale yellow needles (6.5g; 79.7%), m.p. 251°C.

Analysis : Found : C, 62.53%; H, 4.61%

$C_{13}H_{12}O_5$: Requires : C, 62.90%; H, 4.84%

Ethyl-7-allyloxy-8-methylbenzopyran-2H-one-3-carboxylate (125):

A solution of ethyl-7-hydroxy-8-methylbenzopyran-2H-one-3-carboxylate (4g, 16.1mmol) in dry acetone (100ml) was refluxed with fused K_2CO_3 (15g, 0.11mole) and allylbromide (2.0ml, 16.1mmol) for 6h. Crude

product which separated on usual work up, was recrystallized from ethanol as pale yellow needles (3.8g; 82.6%), m.p. 139°C.

Analysis : Found : C, 66.51%; H, 5.49%

$C_{16}H_{16}O_5$: Requires : C, 66.67%; H, 5.55%

Ethyl-7-hydroxy-6-allyl-8-methylbenzopyran-2H-one-3-carboxylate (126):

Ethyl-7-allyloxy-8-methylbenzopyran-2H-one-3-carboxylate (2g, 6.9mmol) in N,N-dimethylaniline (16ml) was refluxed for 12h. The reaction mixture was poured into ice-cold HCl and product thus obtained was stirred with dilute alkali for 5min. to remove unreacted starting material, which was then recrystallized from ethanol to give **126** as yellow needles (1.2g; 60.0%), m.p. 170-1°C.

Analysis : Found : C, 66.79%; H, 5.25%

$C_{16}H_{16}O_5$: Requires : C, 66.67%; H, 5.55%

IR(KBr) cm^{-1} : 3378, 1735, 1702, 1605, 1572, 1256

Ethyl-2,9-dimethylfuro(3,2-g)benzopyran-7H-one-6-carboxylate (127):

A mixture of ethyl-7-hydroxy-6-allyl-8-methylbenzopyran-2H-one-3-carboxylate (1.3g, 4.5mmol) in DMF:H_2O ((21:3)ml) was stirred with freshly prepared CuCl (0.5g, 4.5mmol) and palladium chloride (95mg, 0.45mmol) at room temperature for 14h under oxygen atmosphere till complete disappearance of starting material on TLC. After the reaction contents were poured into cold 3N HCl to give the product, which was recrystallized from ethanol as yellow needles (0.8g; 61.5%), m.p. 167-68°C.

Analysis : Found : C, 67.32%; H, 4.92%

$C_{16}H_{14}O_5$: Requires : C, 67.13%; H, 4.89%

IR(KBr) cm^{-1} : 3073, 2998, 2948, 1762, 1702, 1590, 1246, 1155

4-Allyloxy-2-hydroxybenzaldehyde (128) and 2,4-Diallyloxybenzaldehyde (129):

A mixture of 2,4-dihydroxybenzaldehyde (10g, 72.4mmol) in dry acetone (150ml), anhydrous K_2CO_3 (15g, 0.11mole) and allylbromide (8.8ml, 72.4mmol) was refluxed for 5h. Excess of acetone was distilled out after the reaction. The liquid obtained appeared to be a mixture of two products as mono- and di- allyloxybenzaldehyde (12g) from the TLC, which was used as such for Knoevenagel condensation.

Ethyl-2,4-diallyloxy-α-caynocinnamate (130):

Above liquid mixture **128** and **129** (10g) in dry pyridine (10ml), piperidine (0.5ml, 6mmol) and ethylcyanoacetate (6.4ml) was left at 50-60°C for 24h. The reaction mixture was worked out in dilute HCl, showed to be a mixture of two products, which were separated by column chromatography.

The product which showed higher R_f value was eluted out first with petroleum ether and recrystallized from benzene and petroleum ether mixture (80:20) as bright yellow needles (5g), m.p. 96°C.

Analysis : Found : C, 69.13%; H, 6.06%; N, 4.31%

$C_{18}H_{19}O_4N$: Requires : C, 69.01%; H, 6.07%; N, 4.47%

IR(KBr) cm^{-1} : 3088, 2979, 2930, 2220, 1703, 1595, 1500, 1275

7-Allyloxy-3-cyanobenzopyran-2H-one (131):

The second product was eluted out later with benzene, which recrystallized finally from ethanol to give **131** as pale orange needles (3.3g), m.p. 196°C.

Analysis : Found : C, 68.93%; H, 3.72%; N, 6.38%

$C_{13}H_9O_3N$: Requires : C, 68.72%; H, 3.96%; N, 6.17%

IR(KBr) cm^{-1} : 3070, 2985, 2947, 2232, 1741, 1605, 1507, 1252

9-Allyl-6-cyano-2-methyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one (132):

Ethyl-2,4-diallyloxy-α-cyanocinnamate (2g, 6.4mmol) in refluxing DMA (12ml) for 6h gave a solid after usual workup, which was purified by column chromatography using petroleum and benzene mixture (50:50) and recrystallized from ethanol to give product **132** as orange needles (0.7g; 41.2%), m.p. 159°C.

Analysis : Found : C, 71.95%; H, 5.01%; N, 5.38%

$C_{16}H_{13}O_3N$: Requires : C, 71.91%; H, 4.87%; N, 5.24%

IR(KBr) cm^{-1} : 3071, 2982, 2950, 2228, 1742, 1620, 1576, 1279, 1240

9-(1′-propenyl)-6-cyano-2-methyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one (133):

9-Allyl-6-cyano-2-methyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one (0.5g, 1.9mmol) was refluxed with Pd/C (10%, 0.5g) in diphenylether (7ml) for 6h. The reaction mixture was filtered hot and diluted with petroleum ether to give a product, which was recrystallized from excess of ethanol as orange solid (0.25g; 50.0%), m.p. 224°C.

Analysis : Found : C, 71.87%; H, 4.99%; N, 5.12%

$C_{16}H_{13}O_3N$: Requires : C, 71.91%; H, 4.87%; N, 5.24%

IR(KBr) cm^{-1} : 3078, 2985, 2947, 2226, 1737, 1618, 1574, 1275, 1235

4-Benzyloxy-2-hydroxybenzaldehyde (134):

A mixture of 2,4-dihydroxybenzaldehyde (5g, 36.2mmol) in dry acetone (80ml), anhydrous K_2CO_3 (15g, 0.11mole), benzylchloride (4.6ml, 36.2mmol) and few crystals of potassium iodide to enhance the rate of reaction, was refluxed for 5h. After the reaction acetone was filtered and distilled off. The obtained product was purified by column chromatography using petroleum ether and recrystallized from ethanol as colourless crystals (6.1g; 73.4%), m.p. 81-82°C.

Analysis	:	Found	:	C, 73.91%;	H, 5.42%
$C_{14}H_{12}O_3$	:	Requires	:	C, 73.68%;	H, 5.26%

2-Allyloxy-4-benzyloxybenzaldehyde (135):

4-Benzyloxy-2-hydroxybenzaldehyde (1.5g, 6.6mmol) in dry acetone (50ml), fused K_2CO_3 (10g, 72.4mmol) and allylbromide (0.8ml, 6.6mmol) were refluxed for 12h. After the reaction excess of acetone was distilled to give a solid, which recrystallized finally from ethanol to give **135** as colourless needles (1.4g; 77.8%), m.p. 58°C.

Analysis	:	Found	:	C, 75.93%;	H, 5.81%
$C_{17}H_{16}O_3$	:	Requires	:	C, 76.12%;	H, 5.97%

Ethyl-2-allyloxy-4-benzyloxy-α-carboethoxycinnamate (136):

A mixture of 2-allyloxy-4-benzyloxybenzaldehyde (1.0g, 3.7mmol) in dry pyridine (2ml), piperidine (0.1ml, 1.2mmol) and diethylmalonate (0.6ml, 3.7mmol) was kept at 50-60°C for 24h. Usual workup resulted in the formation of liquid product, which was purified by column chromatography using petroleum ether as a colourless viscous liquid (1.0g; 66.7%).

Analysis	:	Found	:	C, 69.91%;	H, 6.02%
$C_{24}H_{26}O_6$	:	Requires	:	C, 70.24%;	H, 6.34%

PMR($CDCl_3$): δ 1.20 (t, 6H, 2x-CH_3 in the ester group); 4.25 (q, 4H, 2x-CH_2- in the ester group); 4.45 (d, 2H of -CH_2- in -OC$\underline{H_2}$-CH=CH_2); 5.05 (s, 2H of -CH_2- in -OC$\underline{H_2}$-C_6H_5 at C-4); 5.20-5.45 (m, 2H of -CH_2- in -OCH_2-CH=C$\underline{H_2}$); 5.90-6.15 (m, 1H of -OCH_2-C$\underline{H}$=CH_2); 6.45-6.60 (m, 2H at C-3 and C-5); 7.40 (s, 5H of at -OCH_2-$C_6\underline{H_5}$ at C-4); 7.95 (d, 1H at C-6); 8.10 (s, 1H of β-carbon in cinnamyl chain)

Ethyl-7-benzyloxy-8-allylbenzopyran-2H-one-3-carboxylate (137):

Ethyl-2-allyloxy-4-benzyloxy-α-carboethoxycinnamate (1.0g, 2.4mmol) was refluxed with DMA (6ml) for 10h, which upon treatment with cold dilute

HCl gave solid. It was purified by column chromatography using benzene as eluent and recrystallized from ethanol to give the product as yellow needles (0.65g; 72.2%), m.p. 132°C.

Analysis : Found : C, 72.69%; H, 5.31%

$C_{22}H_{20}O_5$: Requires : C, 72.53%; H, 5.49%

Ethyl-2,4-diallyloxy-α-carboethoxycinnamate (138):

The liquid mixture of mono- and di- allyloxybenzaldehyde **128**, **129** (12g) was left for 24h with dry pyridine (12ml), piperidine (0.5ml, 6mmol) and diethylmalonate (10.8ml). After usual workup, mixture of two products was obtained, which were separated by column chromatography. The product, which eluted from petroleum ether was identified **138** as thick colourless liquid (5.5g).

Analysis : Found : C, 66.59%; H, 6.71%;

$C_{20}H_{24}O_6$: Requires : C, 66.67%; H, 6.67%;

PMR($CDCl_3$): δ 1.20 (t, 6H, 2x-CH_3 in the ester group); 4.25 (q, 4H, 2x-CH_2- in the ester group); 4.45 (d, 4H, 2x-CH_2- of -OCH_2-$CH=CH_2$); 5.15 (m, 4H, 2x-CH_2- of -OCH_2-$CH=CH_2$); 5.70-6.10 (m, 2H, 2x-CH- of -OCH_2-$CH=CH_2$); 6.30 (m, 2H at C-3 and C-5); 7.20 (d, J = 9Hz, 1H at C-6); 7.95 (s, 1H of β-carbon in cinnamyl chain)

The product, which eluted with mixture of petroleum ether and benzene (50:50) was confirmed as ethyl-7-allyloxybenzopyran-2H-one-3-carboxylate (106) as yellow needles (4.8g), m.p. 110°C.

Analysis : Found : C, 66.02%; H, 4.94%;

$C_{15}H_{14}O_5$: Requires : C, 65.69%; H, 5.11%;

Ethyl-9-allyl-2-methyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one-6-carboxylate (139):

Ethyl-2,4-diallyloxy-α-carboethoxycinnamate (2g, 5.6mmol) was refluxed with DMA (12ml) for 6h followed by usual work up gave product,

which on recrystallization from ethanol yielded **139** as pale yellow needles (0.6g; 35.3%), m.p. 145°C.

Analysis	:	Found	:	C, 68.89%; H, 5.87%
$C_{18}H_{18}O_5$	:	Requires	:	C, 68.79%; H, 5.73%

Ethyl-9-(1′-propenyl)-2-methyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one-6-carboxylate (140):

Ethyl-9-allyl-2-methyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one-6-carboxylate (0.5g, 1.6mmol) was treated with Pd/C (0.5g) in refluxing diphenylether (7ml) for 6h. The reaction mixture was filtered hot and diluted with petroleum ether to give a product, which was recrystallized from ethanol as yellow needles (0.27g; 54.0%), m.p. 180°C.

Analysis	:	Found	:	C, 68.93%; H, 5.81%
$C_{18}H_{18}O_5$	:	Requires	:	C, 68.79%; H, 5.73%

CRYSTAL DATA AND STRUCTURE REFINEMENT

Crystal Data: $C_{18}H_{18}O_5$; M 314.3; crystal size 0.3 x 0.3 x 0.1mm; T 293K; crystal system – monoclinic; space group $P2_1/n$; a = 7.346(1), b = 16.482(3), c = 12.653(2)A°, β = 92.71(1)°; U = 1530.39A°^{3}; Z = 4; D = 1.358mg/m^3; μ = 0.82mm^{-1}; F(000) = 664; λ(CuKα) = 1.5418A°.

Yellowish plate like single crystals were grown by slow evaporation technique using ethanol as the solvent at room temperature. Cell dimensions were determined by a least-squares procedure applied to the setting angles of 25 reflections in the θ range $11.3<\theta<25.3°$. A total number of 3062 reflections were collected with θ ranging from 2-70°, of which 2829 reflections were found unique ($-8\leq h\leq 8$; $0\leq k\leq 20$; $-15\leq 1\leq 15$) and 1719 reflections were treated as observed with $F_o > 4\sigma(F_o)$. Two standard reflections monitored periodically showed no significant variation in intensity throughout the course of data collection. Data were corrected for Lorentz and polarization factors but no absorption (μ = 0.82mm^{-1}) or extinction corrections were made.

The structure has been solved by direct methods using SHELXS86 program[76]. Of the 23 non-H atoms, only 20 could be located from the E-map. The structure as obtained from SHELXS86 was subjected to full-matrix least-squares refinement using SHELXL93 software[77]. A riding model was used in their refinement (C-H=0.96 A°). Goodness of fit was 1.254. The final cycle of refinement converged the reliability index R to 0.056 and weighted-R(F^2)=0.165. The maximum positive and negative electron density ($\Delta\rho$) in final difference Fourier map ranges from 0.25 to -0.24eA$^{\circ -3}$.

Tables of atomic coordinates and equivalent isotropic parameters, Anisotropic temperature factors, bond distances and bond angles are presented for **140**. **[Table II.1-II.4]**

E-, Z- Ethyl-2,4-diallyloxy-α-acetylcinnamate (141a, 141b):

A mixture of **128** and **129** (10g) in dry pyridine (10ml) was kept with ethylacetoacetate (7.3ml) for 24h using piperidine (0.3, 3.6mmol) as a base. Mixture of three products was obtained after usual work up, which were separated by column chromatography. The isomeric products eluted out from petroleum ether were assigned **141a**, **141b** as yellow viscous liquid (4.1g).

Analysis : Found : C, 68.76%; H, 6.31%

$C_{19}H_{22}O_5$: Requires : C, 69.09%; H, 6.67%

Elution of the column chromatography with mixture of petroleum ether and benzene (50:50) gave 7-allyloxy-6-acetylbenzopyran-2H-one (117), which was recrystallized from ethanol as yellow needles (3.2g), m.p. 153°C.

Analysis : Found : C, 68.91%; H, 5.04%

$C_{14}H_{12}O_4$: Requires : C, 68.85%; H, 4.92%

9-Allyl-6-acetyl-2-methyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one (142):

Isomeric mixture of **141a** and **141b** (2g) was refluxed with N,N-DMA for 6h, on usual workup gave product, which upon recrystallization with ethanol afforded **142** as yellow needles (0.15g), m.p. 151°C.

Table II.1

Atomic coordinates and equivalent isotropic thermal parameters (A^{o2})

Atom	X	Y	Z	Ueq*
O1	0.4571(3)	0.0037(1)	0.2961(2)	0.051(1)
C2	0.4647(6)	0.0917(2)	0.3153(3)	0.063(1)
C3	0.3632(5)	0.1312(2)	0.2212(2)	0.054(1)
O4	0.2001(3)	0.1279(1)	-0.0045(1)	0.036(1)
C5	0.1236(4)	0.1302(2)	-0.1088(2)	0.035(1)
O5	0.0716(3)	0.1945(1)	-0.1379(2)	0.050(1)
C6	0.1188(4)	0.0523(2)	-0.1633(2)	0.031(1)
C7	0.1767(4)	-0.0158(2)	-0.1139(2)	0.033(1)
C8	0.3063(4)	-0.0865(2)	0.0455(2)	0.035(1)
C9	0.3798(4)	-0.0867(2)	0.1491(2)	0.034(1)
C10	0.2467(4)	-0.0170(2)	-0.0080(2)	0.032(1)
C11	0.3880(4)	-0.0088(2)	0.1956(2)	0.035(1)
C12	0.3333(4)	0.0621(2)	0.1466(2)	0.034(1)
C13	0.2583(4)	0.0585(2)	0.0440(2)	0.032(1)
C14	0.0488(4)	0.0423(2)	-0.2764(2)	0.036(1)
O14	0.0395(4)	-0.0232(1)	-0.3181(2)	0.061(1)
O15	0.0000(3)	0.1111(1)	-0.3226(1)	0.046(1)
C16	-0.0724(5)	0.1038(2)	-0.4307(2)	0.058(1)
C17	-0.1038(3)	0.1847(1)	-0.4759(2)	0.084(2)
C18	0.4436(3)	-0.1622(1)	0.1973(2)	0.043(1)
C19	0.5370(4)	-0.1735(2)	0.2882(2)	0.047(1)
C20	0.6047(5)	-0.2546(2)	0.3268(3)	0.062(1)
C21	0.4157(7)	0.1109(2)	0.4191(3)	0.090(2)

* $Ueq = (1/3)\Sigma i\Sigma j Uij\ \alpha i^*\alpha j^* ai.aj.$

Table II.2

Anisotropic temperature factors (A^{o2}) for non-hydrogen atoms

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	0.073(2)	0.041(1)	0.038(1)	-0.005(1)	-0.003(1)	0.005(1)
C2	0.094(3)	0.045(2)	0.049(2)	-0.003(1)	-0.007(2)	0.011(2)
C3	0.071(2)	0.045(2)	0.044(2)	-0.011(1)	-0.011(2)	0.006(2)
O4	0.041(1)	0.033(1)	0.033(1)	-0.001(1)	-0.001(1)	0.002(1)
C5	0.028(2)	0.036(1)	0.041(1)	-0.004(1)	0.004(1)	0.001(1)
O5	0.058(2)	0.038(1)	0.053(1)	-0.001(1)	-0.010(1)	0.009(1)
C6	0.022(1)	0.036(1)	0.035(1)	-0.003(1)	0.003(1)	-0.005(1)
C7	0.026(2)	0.032(1)	0.040(2)	-0.006(1)	0.005(1)	-0.002(1)
C10	0.024(2)	0.036(1)	0.036(1)	-0.005(1)	0.010(1)	-0.001(1)
C8	0.033(2)	0.026(1)	0.048(2)	-0.002(1)	0.012(1)	0.001(1)
C9	0.030(2)	0.038(1)	0.036(1)	0.002(1)	0.004(1)	0.001(1)
C11	0.027(2)	0.044(1)	0.033(1)	-0.001(1)	0.003(1)	-0.003(1)
C12	0.034(2)	0.038(1)	0.031(1)	-0.001(1)	0.006(1)	0.002(1)
C13	0.021(1)	0.033(1)	0.041(1)	0.003(1)	0.008(1)	-0.001(1)
C14	0.027(2)	0.042(2)	0.039(1)	-0.003(1)	0.001(1)	0.001(1)
O14	0.086(2)	0.052(1)	0.043(1)	-0.008(1)	-0.015(1)	0.004(1)
O15	0.056(1)	0.044(1)	0.037(1)	0.001(1)	-0.007(1)	-0.001(1)
C16	0.073(3)	0.061(2)	0.038(2)	-0.001(1)	-0.007(2)	-0.003(2)
C17	0.120(4)	0.063(2)	0.064(2)	0.014(2)	-0.029(2)	-0.001(2)
C18	0.036(2)	0.042(2)	0.050(2)	0.001(1)	0.005(1)	0.003(1)
C19	0.044(2)	0.048(2)	0.051(2)	0.011(1)	0.002(1)	0.004(1)
C20	0.048(2)	0.055(2)	0.083(3)	0.023(2)	0.004(2)	0.005(2)
C21	0.152(5)	0.061(2)	0.056(2)	-0.010(2)	0.004(3)	-0.005(3)

Table II.3

Bond distances (A°) for non-hydrogen atoms

O1-C2	1.471(4)	C10-C13	1.408(4)
O1-C11	1.362(3)	C8-C9	1.394(4)
C2-C3	1.521(5)	C9-C11	1.412(4)
C2-C21	1.414(5)	C9-C18	1.454(4)
C3-C12	1.489(4)	C11-C12	1.374(4)
O4-C5	1.410(3)	C12-C13	1.387(4)
O4-C13	1.358(3)	C14-O14	1.202(4)
C5-O5	1.180(3)	C14-O15	1.318(3)
C5-C6	1.457(4)	O15-C16	1.449(3)
C6-C7	1.344(4)	C16-C17	1.465(4)
C6-C14	1.507(4)	C18-C19	1.324(3)
C7-C10	1.412(4)	C19-C20	1.500(5)
C10-C8	1.391(4)		

Table II.4

Bond angles (°) for non-hydrogen atoms

C2-O1-C11	108.2(2)	C8-C9-C11	113.4(2)
O1-C2-C21	111.4(3)	C11-C9-C18	126.6(3)
O1-C2-C3	106.2(3)	O1-C11-C9	122.2(2)
C3-C2-C21	119.6(3)	C9-C11-C12	125.4(3)
C2-C3-C12	102.8(2)	O1-C11-C12	112.4(2)
C5-O4-C13	123.3(2)	C3-C12-C11	109.5(3)
O4-C5-C6	114.8(2)	C11-C12-C13	118.7(2)
O4-C5-O5	115.2(2)	C3-C12-C13	131.8(2)
O5-C5-C6	130.1(3)	C10-C13-C12	119.2(2)
C5-C6-C14	123.1(2)	O4-C13-C12	119.3(2)
C5-C6-C7	121.0(3)	O4-C13-C10	121.5(3)
C7-C6-C14	115.9(2)	C6-C14-O15	113.6(2)
C6-C7-C10	123.1(2)	C6-C14-O14	121.7(3)
C7-C10-C13	116.2(2)	O14-C14-O15	124.7(3)
C7-C10-C8	124.4(2)	C14-O15-C16	115.3(2)
C8-C10-C13	119.3(3)	O15-C16-C17	109.7(2)
C10-C8-C9	124.0(2)	C9-C8-C19	128.9(2)
C8-C9-C18	120.0(2)	C18-C19-C20	123.9(3)

Analysis : Found : C, 71.67%; H, 5.73%

$C_{17}H_{16}O_4$: Requires : C, 71.83%; H, 5.63%

PMR($CDCl_3$): δ 1.65 (d, J = 7Hz, 3H of $-CH_3$ at C-2); 2.75 (s, 3H of $-COCH_3$ at C-6); 3.15-3.55 (m, 2H at C-3); 3.40 (d, 2H of $-C\underline{H}_2-CH=CH_2$ at C-9); 5.00-5.30 (m, 2H of $-CH_2-CH=C\underline{H}_2$ at C-9 overlapped with 1H at C-2); 6.00 (m, 1H of $-CH_2-C\underline{H}=CH_2$ at C-9); 7.25 (s, 1H at C-8); 8.40 (s, 1H at C-7)

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