CHAPTER II

SECTION I

SYNTHESIS OF PYRANOCOUMESTAN DERIVATIVES

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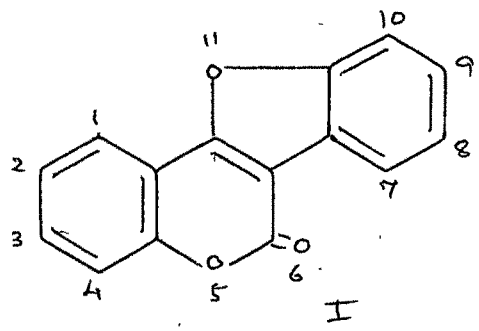
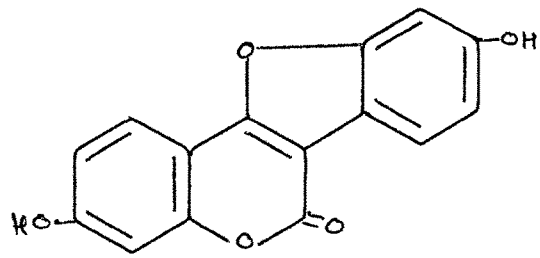
THEORETICAL

Coumestans are a class of naturally occurring compounds[1-9] of heterocyclic four-ring system, also known as benzofuro-a-benzopyrone or coumarinobenzofuran. The simple coumestan or 6H-benzofuro(3,2-c)benzopyran-6-one[10] is represented as (I).

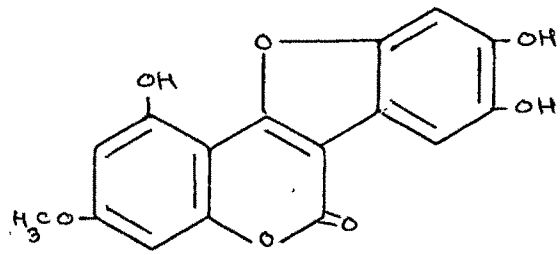


I

Coumesterol (II) is the estrogenic constituent of Ladino clover[11]. Wedelolactone[13] (III), Erosnin[4] (IV), Medicagol[5] (V), Trifolilol[6] (VI), Psoralidin[7] (VII), Sativol[8] (VIII) and Lucernol[9] (IX) are the naturally occurring coumestan derivatives. This class is of particular interest because of the estrogenic properties[12-16] and has relationship to pathogenic attack of plant[17].



II



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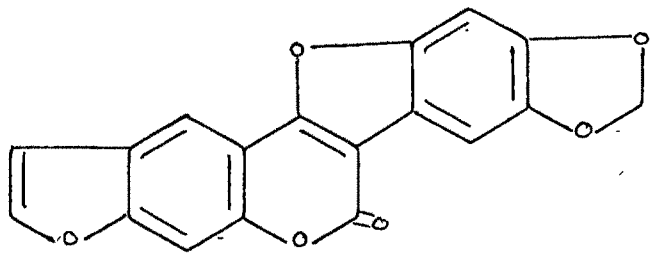

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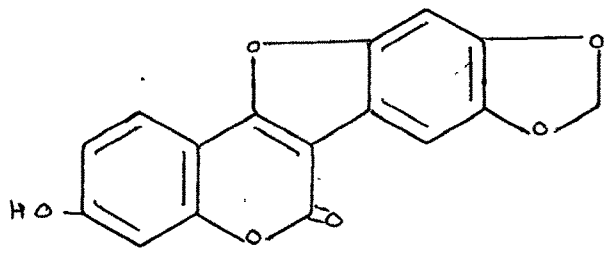

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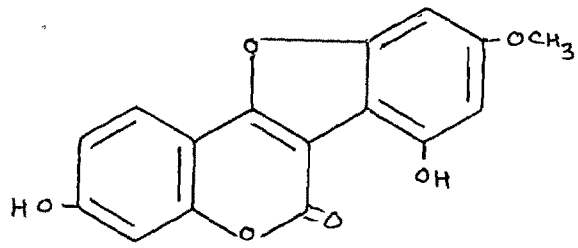

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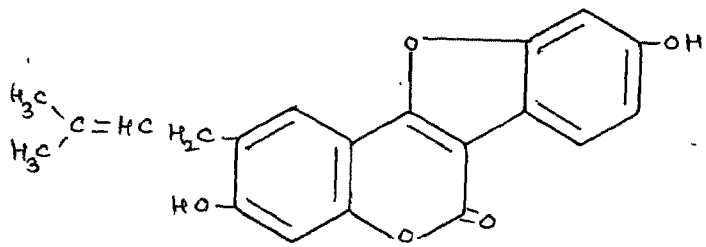
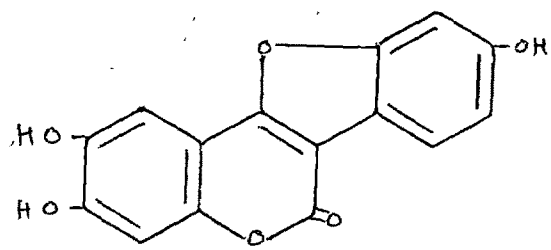
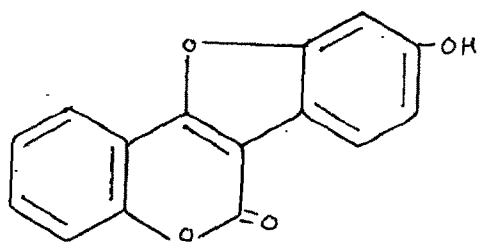


VII



VIII



IX

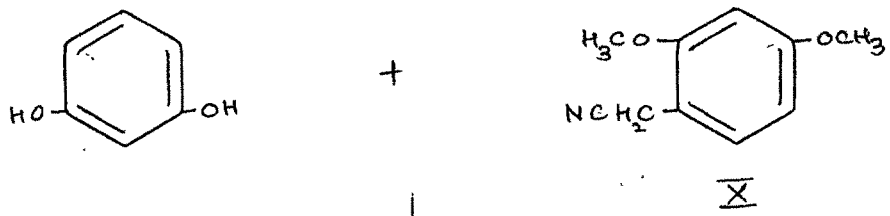
Few naturally occurring substituted coumestans have been synthesised earlier[18-24]. Emerson and Bickoff[25] condensed 2,4-dimethoxyphenyl acetonitrile (X) with resorcinol and obtained α-(2,4-dimethoxyphenyl)-2,4-dihydroxy-acetophenone (XI), which on treatment with methylchloroformate gave 3-(2,4-dimethoxyphenyl)-4,7-dihydroxycoumarin (XII). This was cyclised by heating with aniline hydrochloride to coumestrol (II) in overall yield of about 17 %.

Mentzer et al.[26] synthesised coumestan or 6-oxo-6H-benzofuro(3,2-c)benzopyran (I) by thermal condensation of equimolar amounts of o-methoxyphenylmalonate with phenol giving 3-(2-methoxyphenyl)4-hydroxycoumarin (XIII) followed by the cyclisation with pyridine hydrochloride.

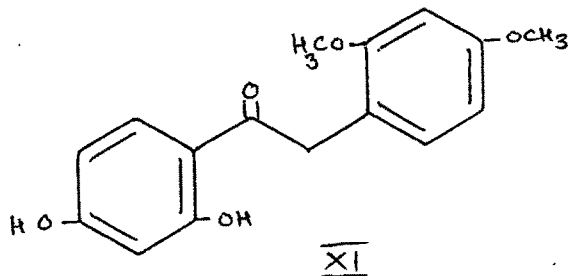
Coumestan (I) was also synthesised by Chatterjee and Roy[27] by condensing o-methoxyphenyl acetonitrile (XIV) with ethyl-o-methoxybenzoate (XV) in the presence of sodium ethoxide and treating them intermediate ketonitrile (XVI) with hydrobromic acid.

Jurd[28] synthesised coumestrol and related compounds by hydrogen peroxide oxidation of appropriately substituted 2'-hydroxy-3-methoxyflavylium salts. Yoshiyuki Kawase[29] synthesised the same by different route.

Govindachari and co-workers[30,31] isolated Wedelolactone (III) from the leaves of Wedelia calendulacea (compositae) and they synthesised substituted wedelolactone

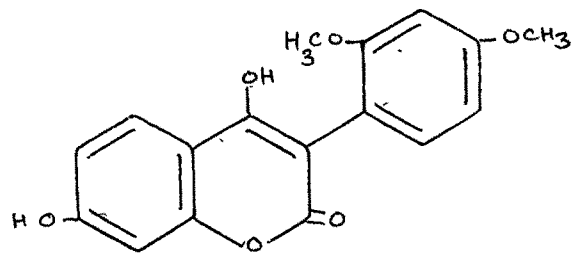


X



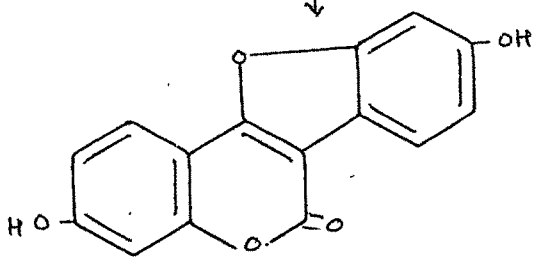
XI

Methyl chloroformate



XII

$C_6H_5NH_2 \cdot HCl$



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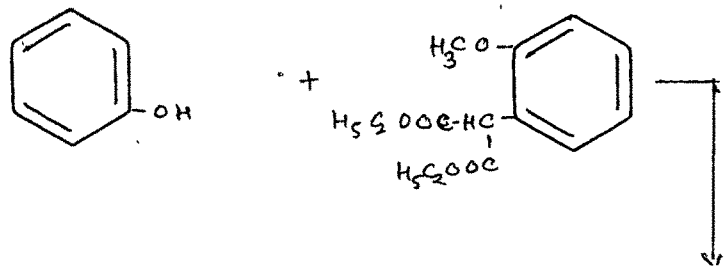
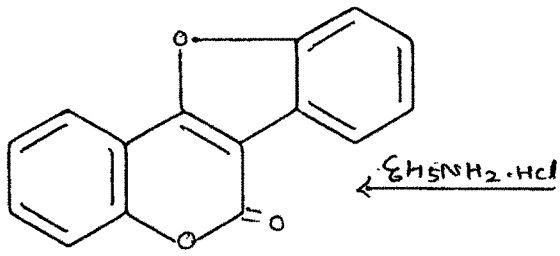
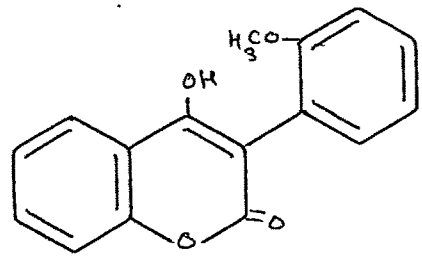
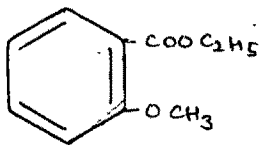


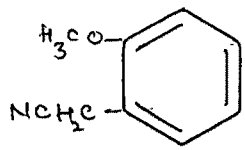




I

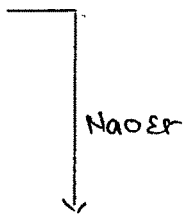
XIII

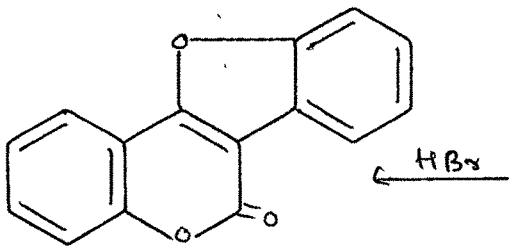


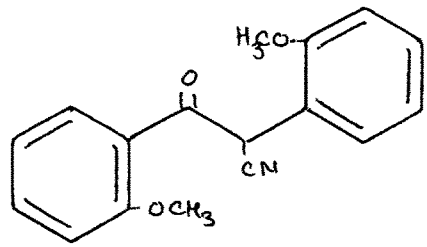


XV

XIV

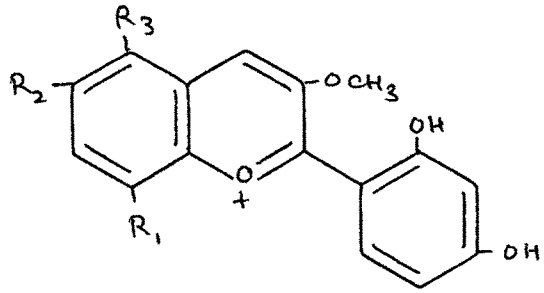




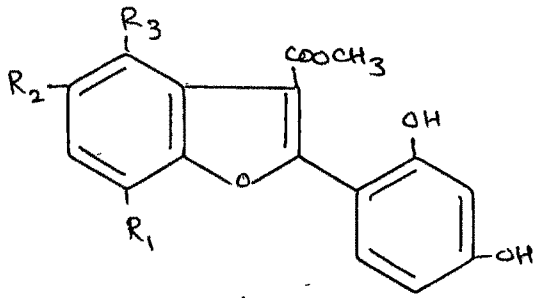


I

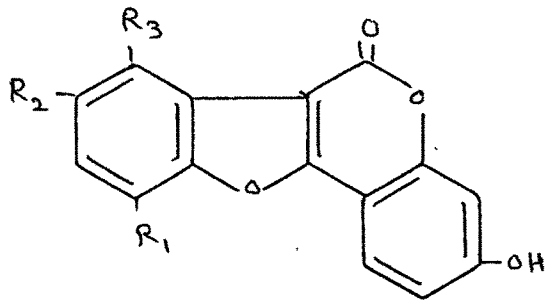
XVI



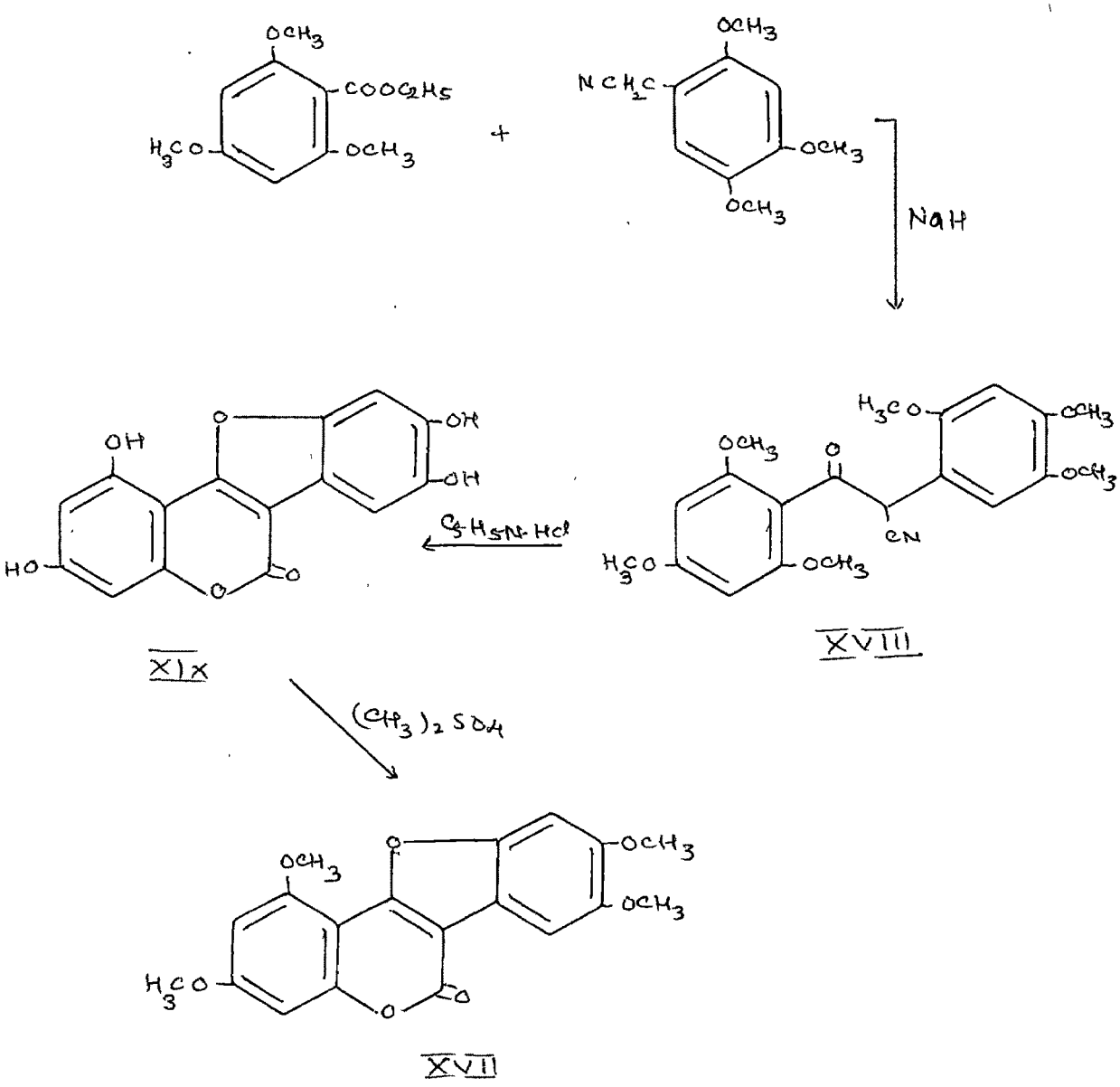
H_2O_2 in methanol



Acidification

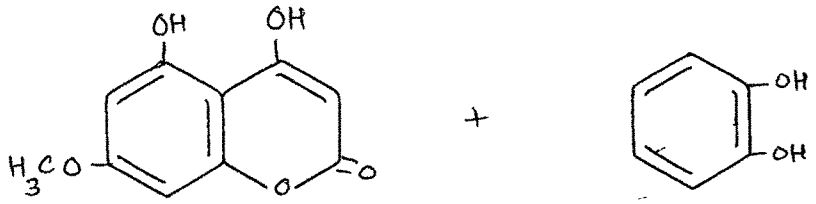


derivative. Chatterjea and Prasad[32] reported the synthesis of tri-O-methylwedelolactone (XVII). The ketonitrile (XVIII), obtained by condensation of 2,4,5-trimethoxybenzyl cyanide and ethyl-2,4,6-trimethoxybenzoate in the presence of sodium hydride, was treated with pyridine hydrochloride to yield (XIX), which was readily methylated to trimethoxy-wedelolactone (XVII).

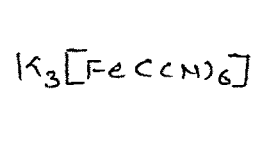


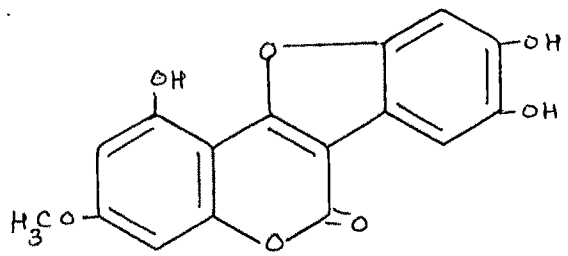
XIX XVIII XVII

Wanzlick and co-workers[33] prepared wedelolactone (III) by dehydrogenative coupling of catechol with 4,5-dihydroxy-7-methoxycoumarin (XX) in the presence of potassium ferricyanide or potassium iodate.



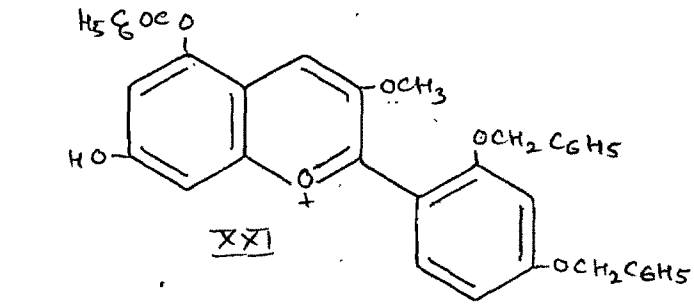
XX



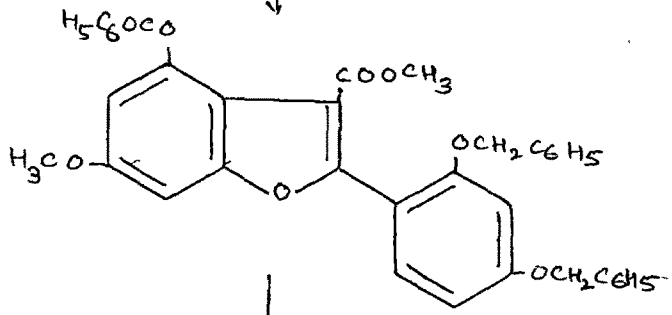


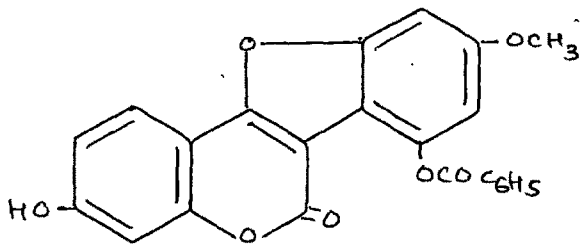
III

Trifolilol (VI) was isolated from Ladino clover by Jurd and co-workers[34] and confirmed the structure. They have synthesised it by peroxide oxidation of 5-benzoyloxy--7-hydroxy-3-methoxy-2',4'-dibenzoyloxyflavylium chloride (XXI), followed by methylation and debenzylation to give 7-benzoyloxy--3-hydroxy-9-methoxycoumestan (XXII) and subsequent alkaline hydrolysis.



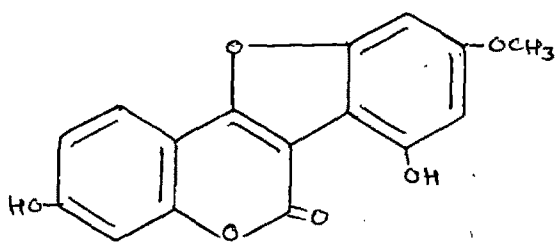
XXI





XXII

alkaline hydrolysis



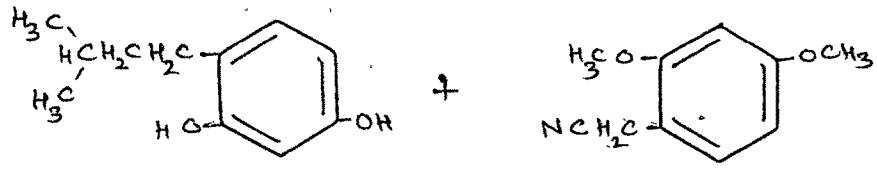
VI

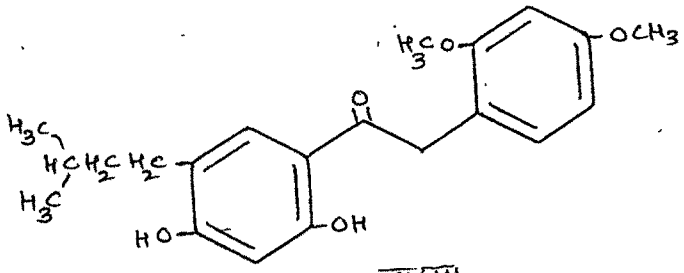
Medicagol (V) was isolated as a mixture with pistatin from alfalfa meal and its synthesis is reported by Jurd[35].

Psoralidine (VII) was first isolated from the pericarp of the seeds of P.Corylifolia by Chakravarti and co-workers[36]. Later Sengupta and co-workers[8] isolated the same from the alcoholic extract of the seed kernal of Psoralea Corylifolia Linn. and proved that it is the isopentenyl derivative of coumestrol.

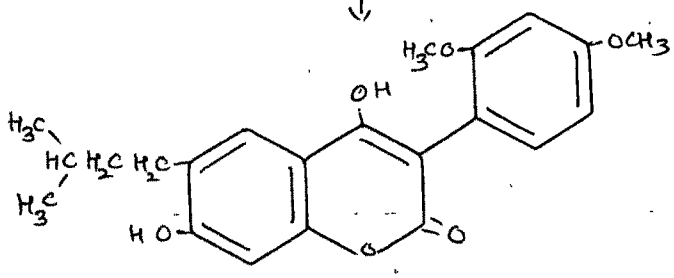
As psoralidin is liable to acids, it has not been synthesised but dihydropsoralidine (XXV) is synthesised by different workers by different methods. Nasipuri and Pyne[37] and Bickoff et al.[16] have reported the synthesis of (XXV). 2,4-Dihydroxy-5-isopentenyl-2,4-dimethoxybenzylketone (XXIII), obtained by Hoesch reaction of 2,4-dimethoxybenzyl cyanide and 4-isopentenylresorcinol, was treated with ethyl chloroformate and then subjected with alkali and then with acid to give 4,7-dihydroxy-6-isopentenyl-3-(2',4'-dimethoxy--phenyl)coumarin (XXIV) which on further treatment with aniline hydrochloride gave dihydropsoralidin (XXV).

They have also reported the synthesis of isopsoralidin (XXVIII). Hoesch condensation of 2,4-dimethoxybenzyl cyanide with 7-hydroxy-2,2-dimethylchroman furnished 2,4-dimethoxybenzyl-7-hydroxy-2,2-dimethylchroman-6-yl-ketone (XXVI) which was converted into the 4-hydroxycoumarin derivative (XXVII) by sodium and ethyl carbonate. This, on treating with aniline hydrochloride gave isopsoralidin (XXVIII).

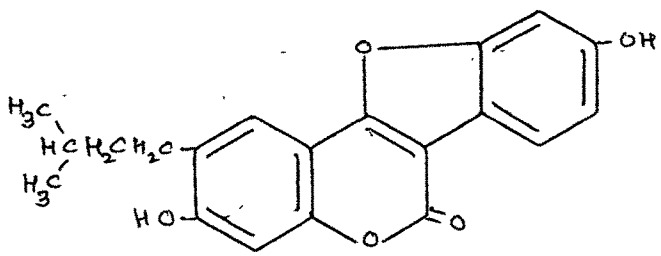




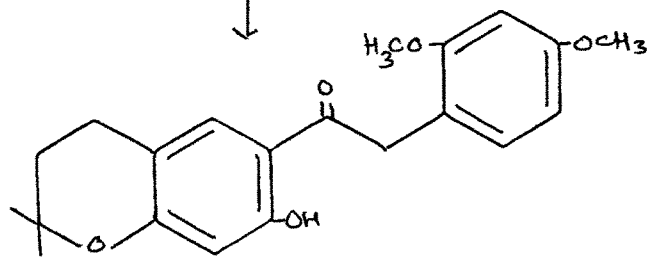
XXIII



XXIV

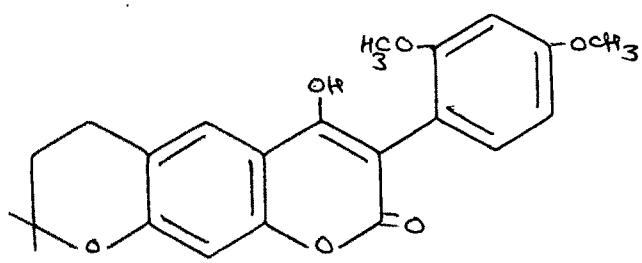


XXV



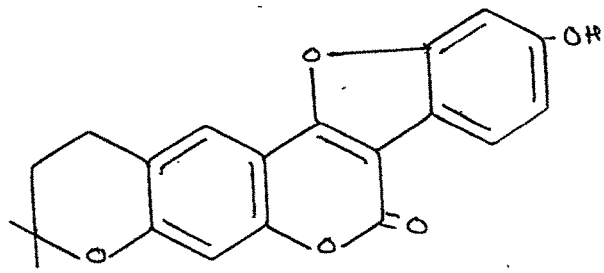
XXVI

Na,
Ethyl carbonate



XXVII

$C_6H_5NH_2 \cdot HCl$



XXVIII

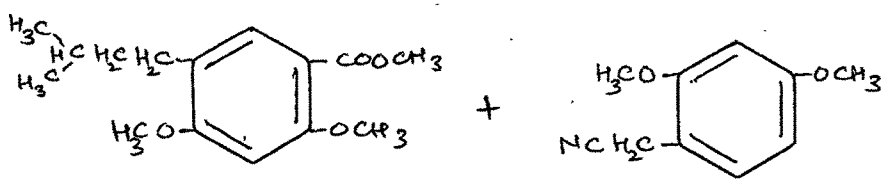
Similarly, they have condensed methyl-2,2-dimethyl-7-methoxychromanbenzoate with 2,4-dimethoxybenzyl cyanide in the presence of sodium hydride followed by the treatment with pyridine hydrochloride to yield isopsoralidin.

Chatterjea, Banerjee and Prasad[38] have prepared dihydropsoralidin (XXV) and isopsoralidin (XXVIII) using the method of Yoshiyuki Kawase[29]. The condensation of methyl--2,4-dimethoxy-5-isopentenylbenzoate and 2,4-dimethoxybenzyl cyanide in the presence of sodium hydride gave α-(2,4-dimethoxy-5-isopentenylbenzoyl)2,4-dimethoxybenzyl cyanide (XXIX) which when reacted with pyridine hydrochloride gave dihydropsoralidin (XXV).

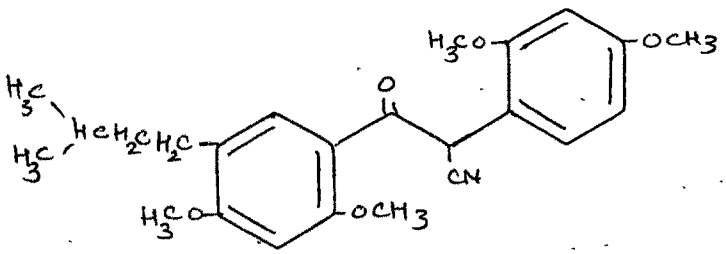
They have also reported the synthesis of isopsoralidin (XXVIII) by condensing methyl-2,3-dimethyl-7--methoxychromanbenzoate (XXX) with 2,4-dimethoxybenzyl cyanide in the presence of sodium hydride to obtain ketonitrile (XXXI) and subsequent treatment with pyridine hydrochloride.

V.K.Karla and co-workers[39] synthesised sativol (VIII) and lucernol (IX) and their methylether derivatives. Simonova and Shamshurin[21] synthesised 7,11-dihydroxycoumestan by peroxide oxidation of 2',4',6'-trihydroxy-3-methoxyflavylium chloride.

Spencer, Knuckles and Bickoff[40] synthesised 7-hydroxy-11,12-dimethoxycoumestan by hydrogen peroxide oxidation of 6,7,2',4'-tetrahydroxyflavylium salt and selective methylation of 7,11,12-trihydroxycoumestan.

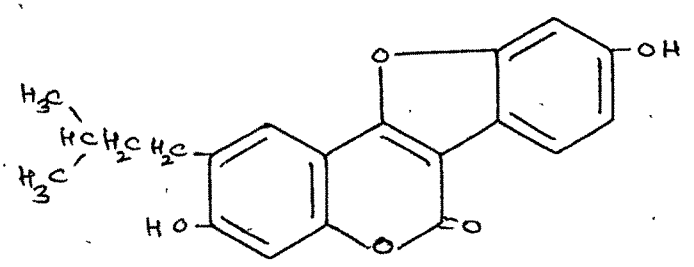


NaH

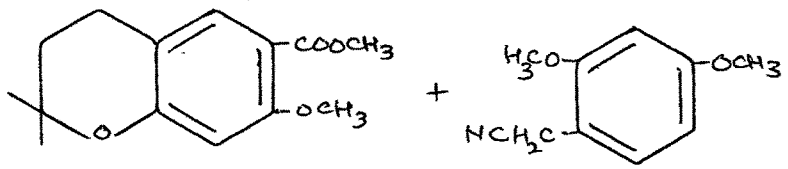


XXIX

$C_5H_5N \cdot HCl$



XXV



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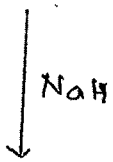
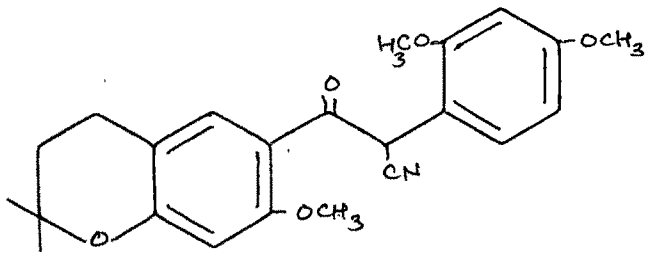
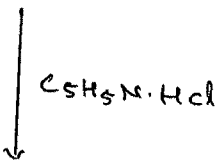
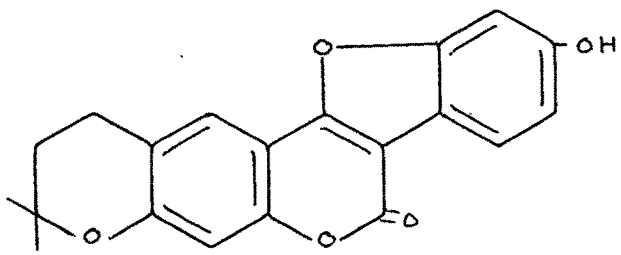




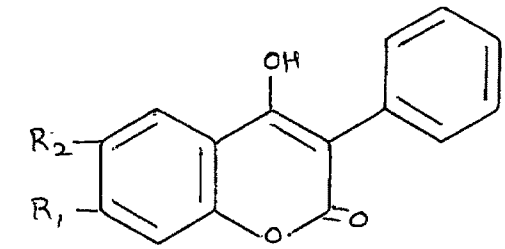
XXXI



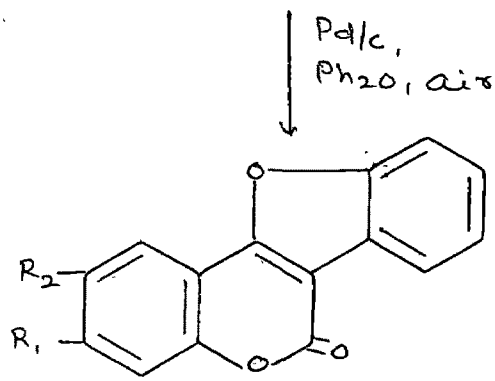


XXVIII

Recently Thomas Kappe and Schmidt[41] reported a new method of synthesis of coumestan derivatives, starting with 4-hydroxy-3-phenylcoumarin derivatives. Cyclodehydrogenation of 4-hydroxy-3-phenylcoumarin derivative (XXXII) occurred when the reaction mixture was refluxed with diphenylether and palladised charcoal (10 %) and air being bubbled through the reaction mixture giving corresponding coumestan derivative (XXXIII).



XXXII



XXXIII

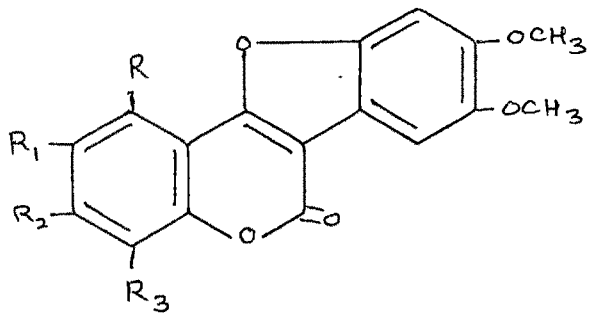
(a) $R_1=R_2=H$

(b) $R_1=CH_3$; $R_2=H$

(c) $R_1=R_2=CH_3$

(d) $R_1=OCH_3$; $R_2=H$

Dholakia and Trivedi[42] synthesised coumestan derivatives by oxidative condensation of catechol with different 4-hydroxycoumarins followed by methylation using the method Wanzlick[33]. They have synthesised 2-methyl-8,9-dimethoxy-6H-benzofuro(3,2-c)benzopyran-6-one (XXXIVa), 2,8,9-trimethoxy-6H-benzofuro(3,2-c)benzopyran-6-one (XXXIVb), 4-methyl-3,8,9-trimethoxy-6H-benzofuro(3,2-c)benzopyran-6--one (XXXIVc), 1,8,9-trimethoxy-6H-benzofuro(3,2-c)benzopyran-6-one (XXXIVd) and 3,4,8,9-tetramethoxy-6H-benzofuro--(3,2-c)benzopyran-6-one (XXXIVe).



XXXI

(a) $R=R_2=R_3=H$; $R_1=CH_3$

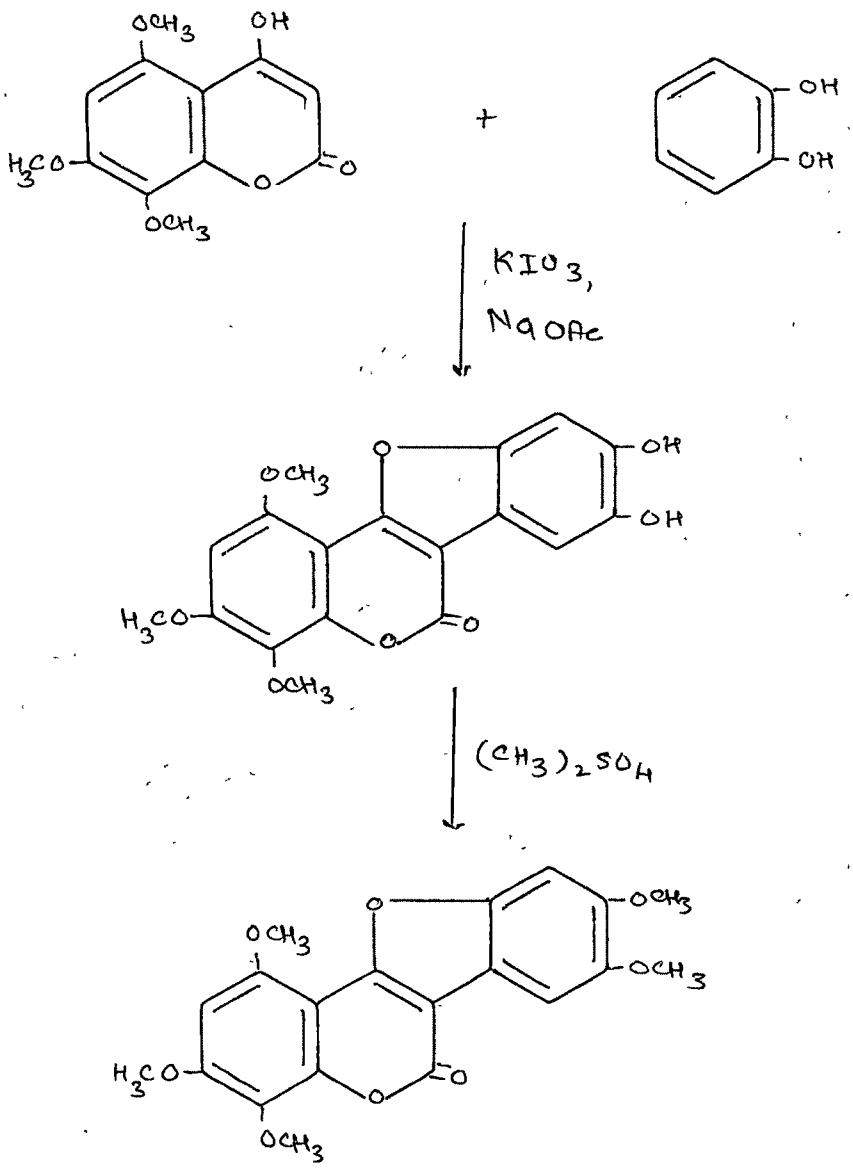
(b) $R=R_2=R_3=H$; $R_1=OCH_3$

(c) $R=R_1=H$; $R_2=OCH_3$; $R_3=CH_3$

(d) $R=OCH_3$; $R_1=R_2=R_3=H$

(e) $R=R_1=H$; $R_2=R_3=OCH_3$

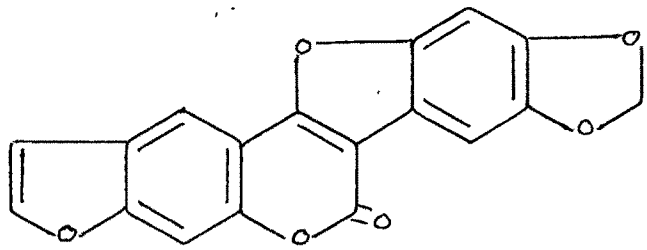
Shaikh and Trivedi[43] synthesised 1,3,4,8,9-pentamethoxy-6H-benzofuro(3,2-c)benzopyran-6-one (XXXV) by oxidative coupling of 5,7,8-trimethoxy-4-hydroxycoumarin with catechol in the presence of potassium iodate and sodium acetate followed by methylation with dimethyl sulphate.



XXXV

Subba Rao et al.[44] have also reported similar type of coumestan derivatives, synthesised using the method of Wanzlick.

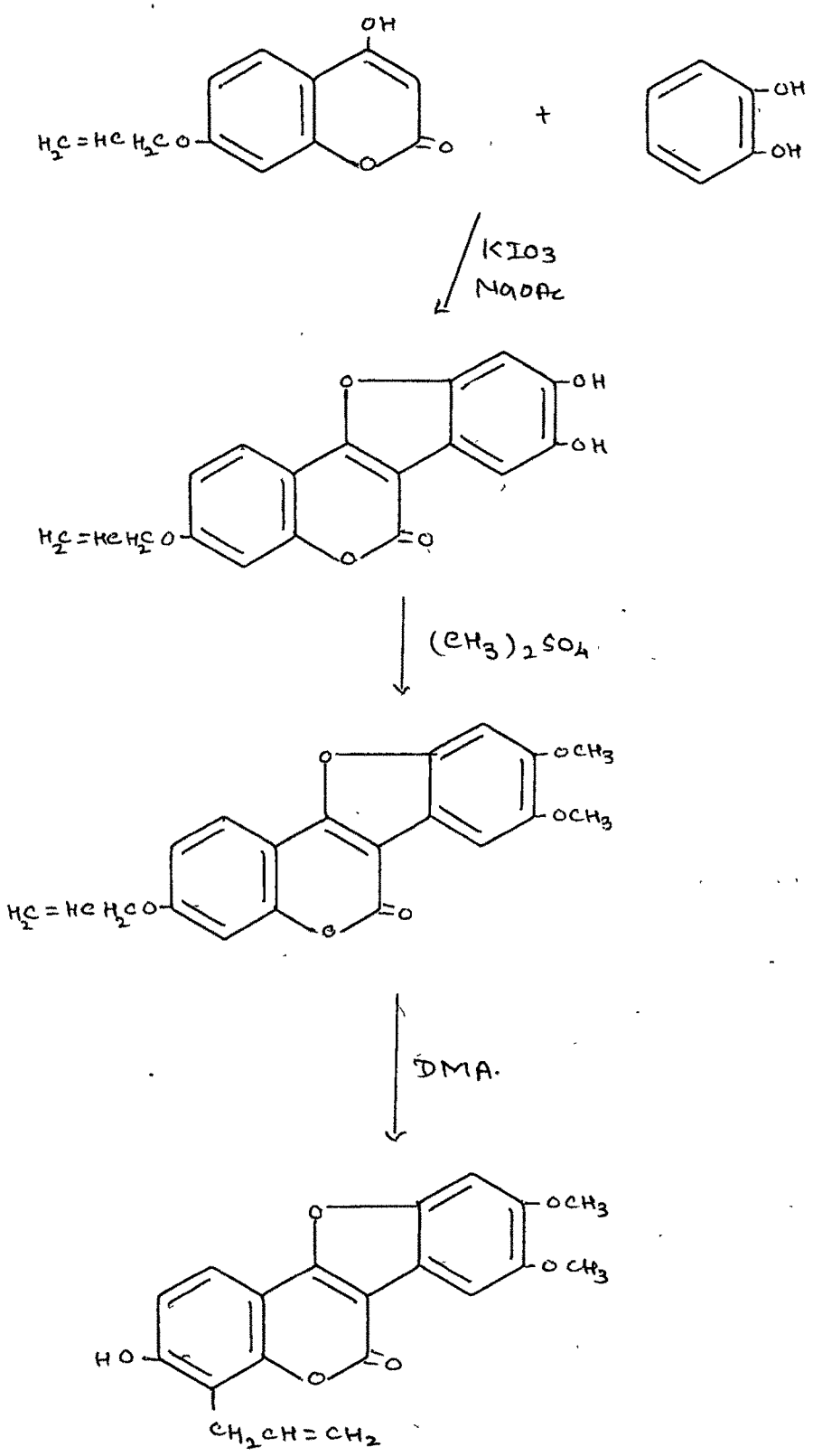
K.Fukui and N.Nakayama[45] synthesised erosnin (XXXVI) by dehydrogenative coupling of 4-hydroxypsoralene and catachol in the presence of potassium ferricyanide according to the method of Wanzlick.

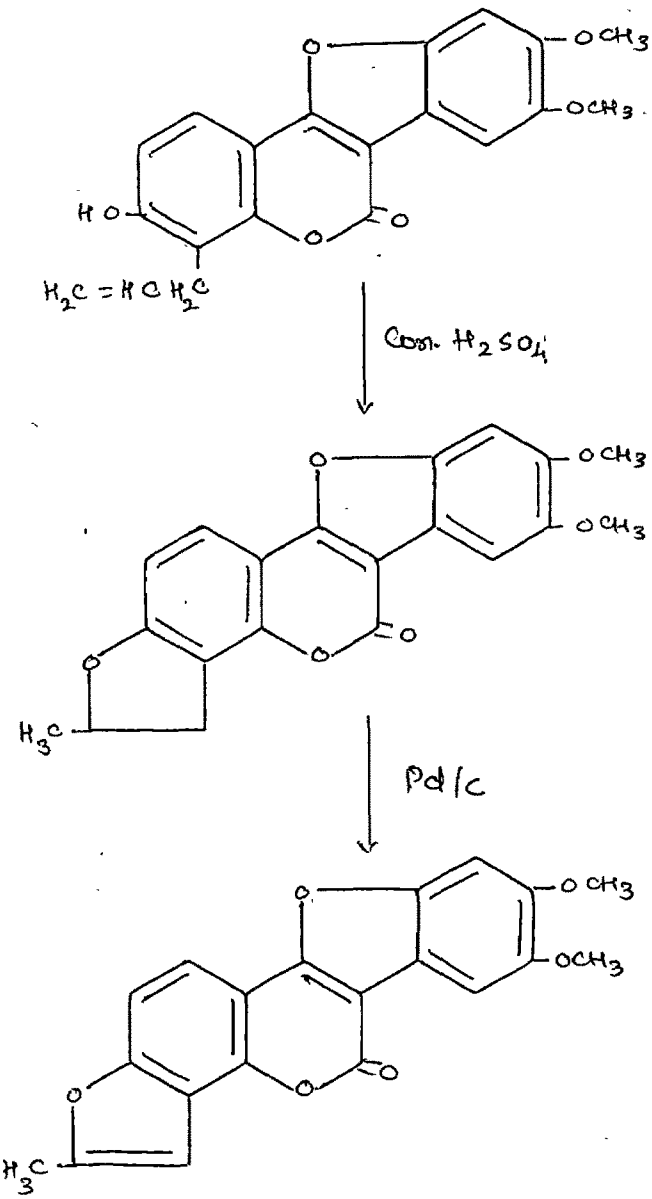


XXXVI

Shah and Trivedi[46] have reported the synthesis of 5'-methyl-8,9-dimethoxyfuro(2,3-h)coumestan, 4,5'-dimethyl--8,9-dimethoxyfuro(3,2-g)coumestan and 5'-methyl-8,9-dimethoxyfuro(2,3-f)coumestan. They synthesised the furocoumestan derivatives by the following route.

7-Allyloxy-4-hydroxycoumarin (XXXVII) on dehydrogenative coupling with catachol, according to the method of Wanzlick, yielded a coumestan derivative. This on Claisen rearrangement followed by cyclisation and dehydrogenation with palladised charcoal (10 %) gave furocoumestan derivative (XXXVIII).


OH
H2C=HC H2C O
O
+
OH
OH
KIO3
NaOAc
O
OH
OH
H2C=HC H2C O
O
O
(CH3)2SO4
O
OCH3
OCH3
H2C=HC H2C O
O
O
DMA.
O
OCH3
O CH3
HO
O
O
CH2CH=CH2



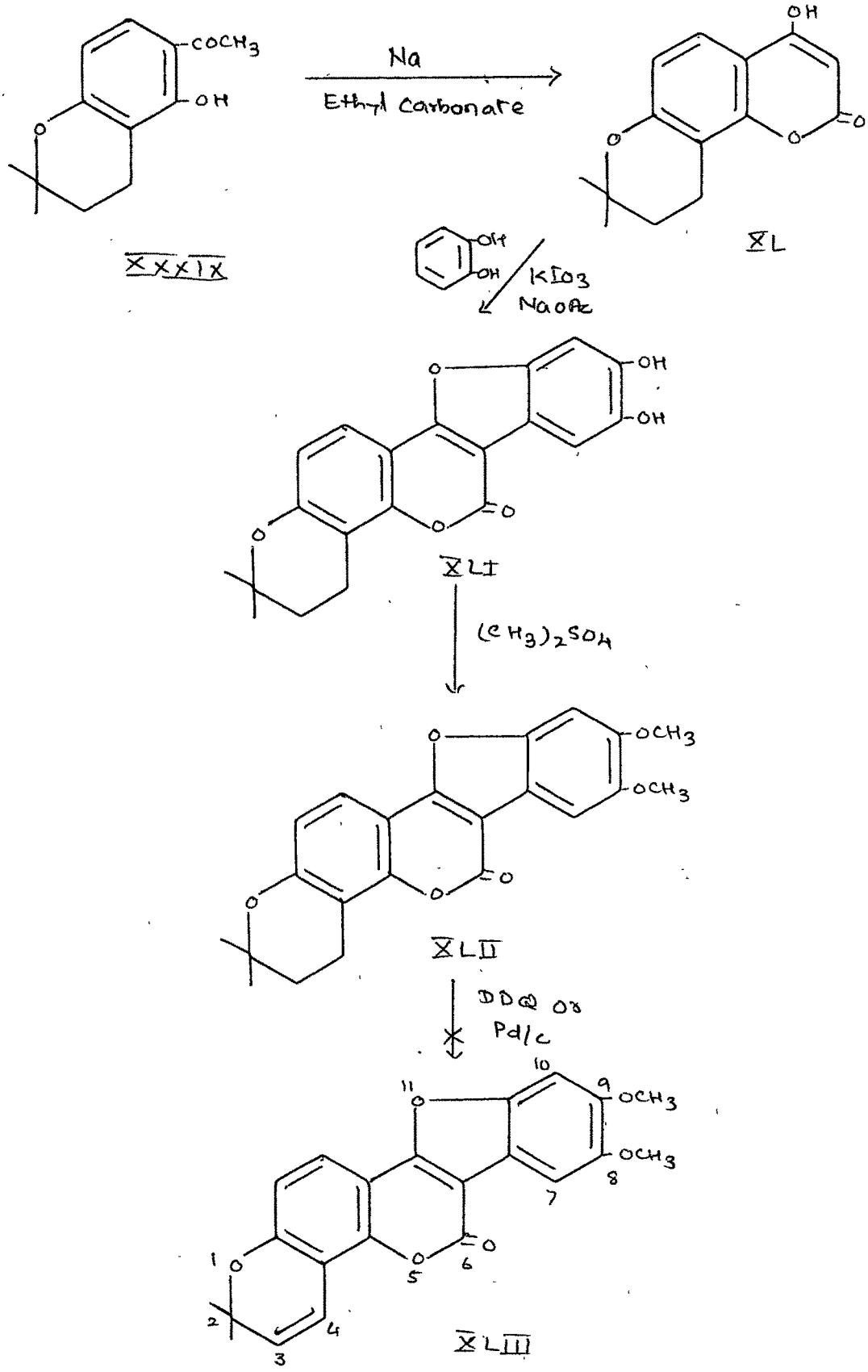
In continuation of the work on coumestan derivatives carried out in this laboratory by Dholakia, Shaikh, Shah and Trivedi, it was thought of interest to synthesise few more coumestan derivatives having pyran ring, to have psoralidin type coumestan derivatives. This type of coumestans are reported earlier.

Synthesis of 8,9-dimethoxy-2,2-dimethylpyrano-(2,3-h)coumestan

Seshadri et al.[47] prenylated resacetophenone to get C-prenylated resacetophenone which were further cyclised to corresponding chromeno derivatives.

3,4-Dihydro-6-acetyl-5-hydroxy-2,2-dimethylchromene (XXXIX), prepared according to Seshadri et al.[47], was treated with diethyl carbonate in the presence of pulversied sodium, according to the method of Boyd and Robertson[48], to give corresponding 2,2-dimethyl-3,4-dihydro-8-hydroxy-6-oxo-6H-pyrano(2,3-h)benzopyran (XL). This on dehydrogenative coupling with catechol in the presence of potassium iodate and sodium acetate gave 8,9-dihydroxy-2,2-dimethyl-3,4-dihydropyrano-(2,3-h)coumestan (XLI).

The above coumestan derivative was then methylated with dimethyl sulphate and anhydrous potassium carbonate in acetone to give 8,9-dimethoxy-2,2-dimethyl-3,4-dihydropyrano-(2,3-h)coumestan (XLII). This on dehydrogenation with DDQ in dry benzene or any other solvent like dioxan or chlorobenzene failed to give corresponding dehydrogenated pyranocoumestan derivative (XLIII).


COCH3
OH
Na
Ethyl Carbonate
OH
O
O
O
XXXIX
XL
OH
OH
KIO3
NaOAc
OH
OH
O
O
O
O
XLI
(CH3)2SO4
OCH3
OCH3
O
O
O
O
XLII
DDQ OR
Pd/C
10
11
9
OCH3
OCH3
8
7
O
1
O
5
6
O
2
4
3
XLIII

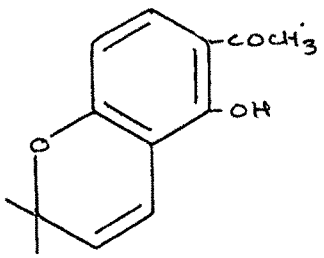
As above compound could not be converted to the title compound by different methods of dehydrogenation, the synthesis of the title compound was finally achieved by the following route.

2,2-Dimethyl-8-hydroxy-6-oxo-6H-pyrano(2,3-h)-benzopyran (XLIV) was prepared from 2,2-dimethyl-6-acetyl-5--hydroxychromene[47] (XLV) by treating it with sodium and diethyl carbonate. 2,2-Dimethyl-8-hydroxy-6-oxo-6H-pyrano-(2,3-h)benzopyran (XLIV) was oxidatively coupled with catechol in the presence of potassium iodate and sodium acetate to give 8,9-dihydroxy-2,2-dimethylpyrano(2,3-h)-coumestan (XLVI), which was methylated to 8,9-dimethoxy--2,2-dimethylpyrano(2,3-h)coumestan (XLIII).

IR (nujol) (XLIII) : 1700 $cm.^{-1}$ (α-pyrone carbonyl stretching frequency), 1365 $cm.^{-1}$ (geminal dimethyl group stretching frequency) and 1280 $cm.^{-1}$ (aromatic ether linkage). A band at 3400 $cm.^{-1}$ is also observed for water.

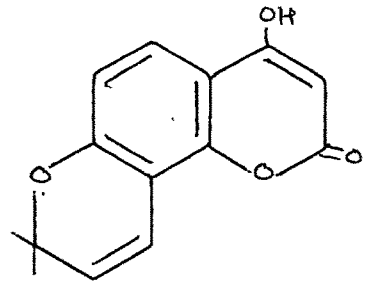
The NMR spectrum of the compound (XLIII) in $CDCl_3$ is as under :-

δ 1.50, singlet, geminal dimethyl group at position-2; 4.00 and 4.02, two singlets, two methoxy groups at positions-8 and -9; 5.80 and 6.85, two doublets, J=9Hz, two protons at positions-3 and -4 and 7.00-7.85, multiplet, four protons aromatic at positions-7, -10, -12 and -13. (Fig. 1).

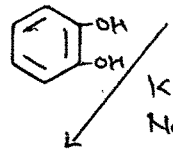


XLV

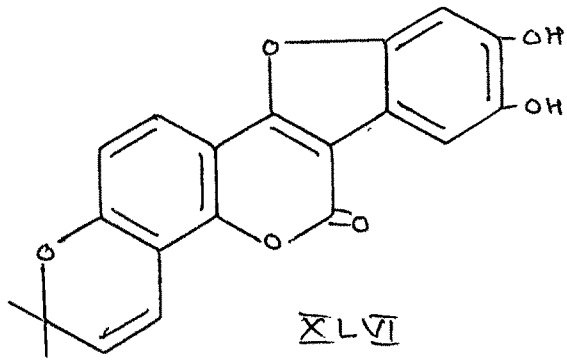
Na
Ethyl Carbonate



XLIV

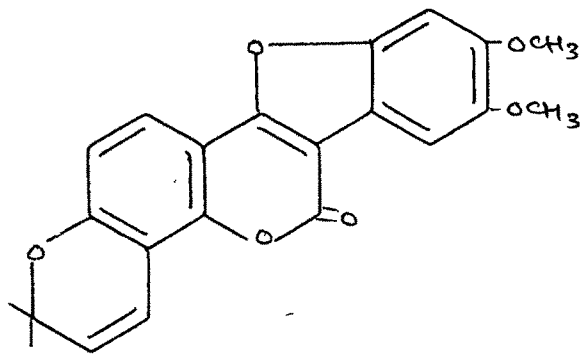


KIO3
NaOAc

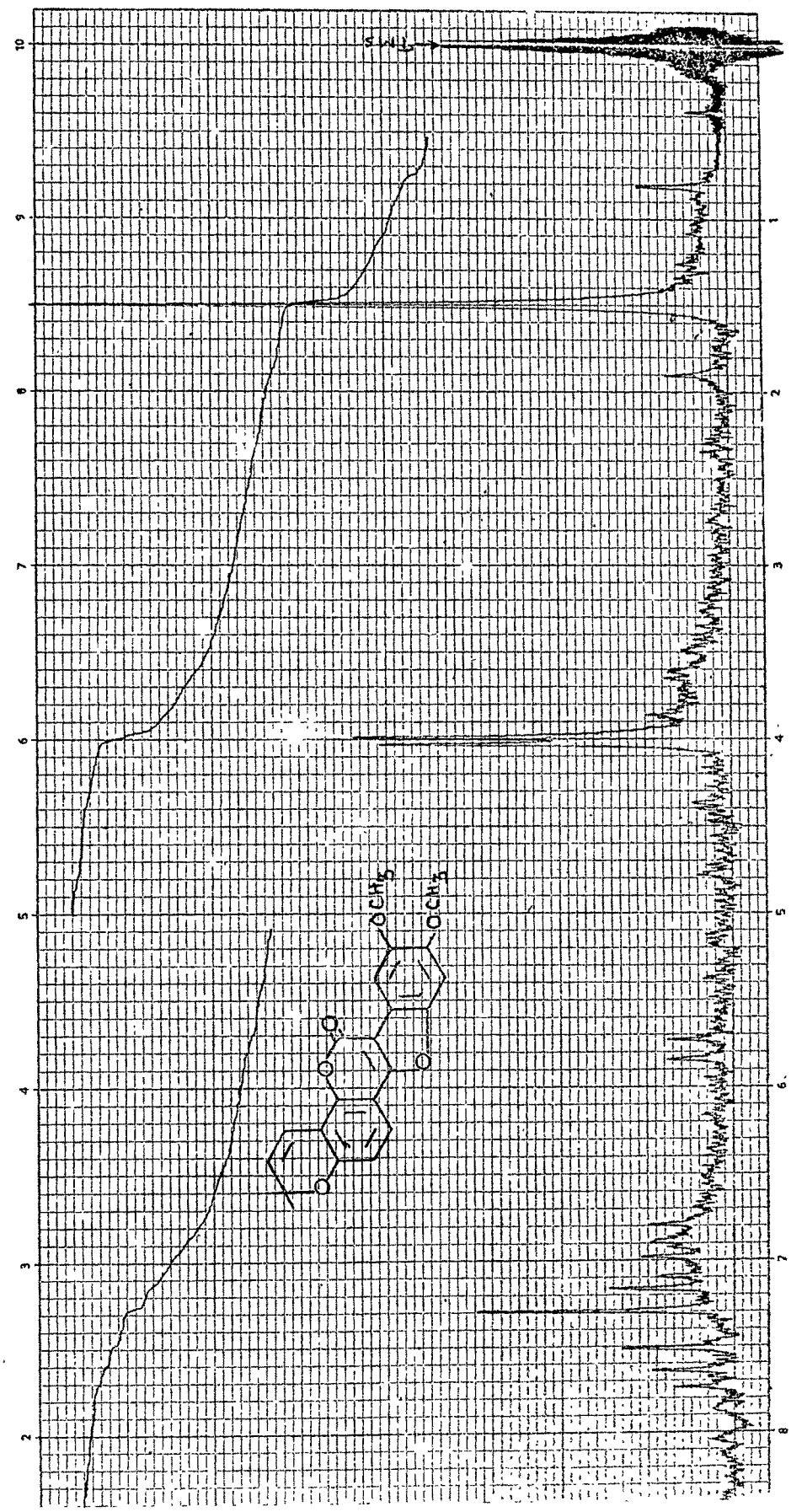


XLVI

$(CH_3)_2SO_4$



XLIII



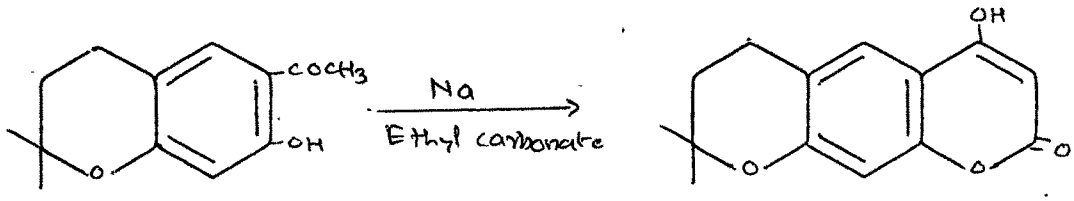
(Fig. 1) : 8,9-Dimethoxy-2,2-dimethylpyrano(2,3-h)coumestan

Synthesis of 8,9-dimethoxy-2,2-dimethylpyrano-(3,2-g)coumestan

3,4-Dihydro-6-acetyl-7-hydroxy-2,2-dimethylchromene (XLVII), prepared according to Seshadri et al.[47], was condensed with diethyl carbonate in the presence pulverised sodium to give 2,2-dimethyl-3,4-dihydro-6-hydroxy-8-oxo-8H-pyrano(3,2-g)-benzopyran (XLVIII). This was coupled oxidatively with catechol in the presence of potassium iodate and sodium acetate to give 8,9-dihydroxy-2,2-dimethyl-3,4-dihydropyrano(3,2-g)coumestan (XLIX). This was then directly methylated to 8,9-dimethoxy-2,2-dimethyl-3,4-dihydropyrano(3,2-g)coumestan (L). The IR spectrum showed a strong band at 1730 $cm.^{-1}$ for α-pyrone carbonyl group and a band at 1370 $cm.^{-1}$ for a geminal dimethyl group.

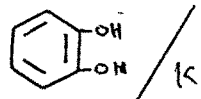
This failed to give its dehydrogenated derivative, 8,9-dimethoxy-2,2-dimethylpyrano(3,2-g)coumestan (LI), by different methods of dehydrogenation. To synthesise this, the following alternative route was adopted :-

2,2-Dimethyl-6-hydroxy-8-oxo-8H-pyrano(3,2-g)-benzopyran (LIII) was prepared from 2,2-dimethyl-6-acetyl-7-hydroxychromene[47] (LII) by treating it with sodium and diethyl-carbonate. (LIII) was coupled oxidatively with catechol in the presence of potassium iodate and sodium acetate to give 8,9-dihydroxy-2,2-dimethylpyrano(3,2-g)coumestan (LIV). This was then methylated with dimethyl sulphate to 8,9-dimethoxy-

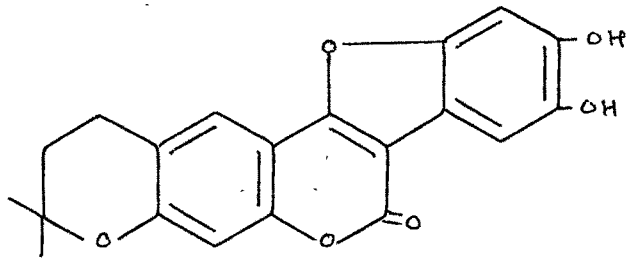


XLVII

XLVIII

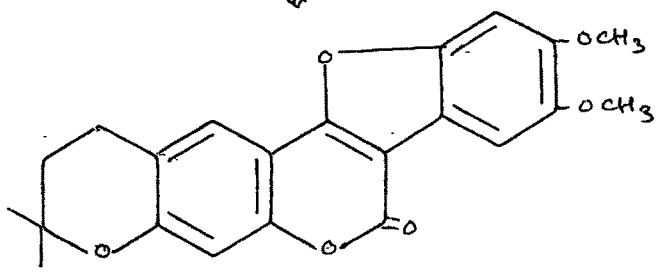


KIO3
NaOAc



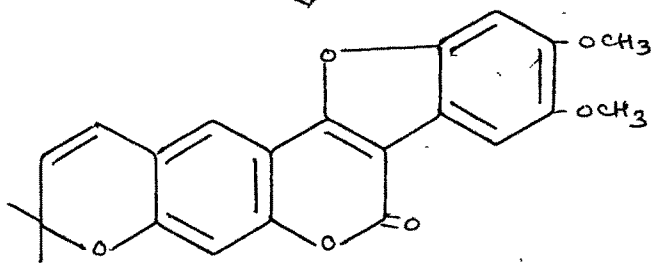
XLIX

$(CH_3)_2SO_4$



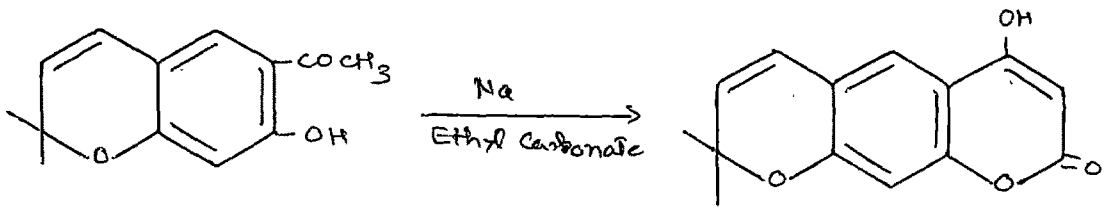
L

DDQ or
Pd/c

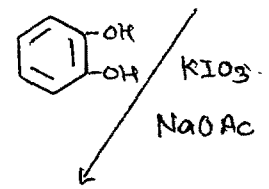


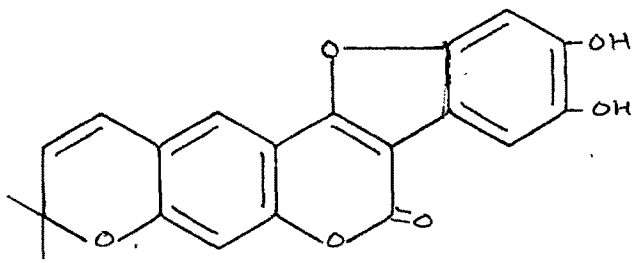
LI

-2,2-dimethylpyrano(3,2-g)coumestan. (LI). The IR spectrum showed bands at 3400 $cm.^{-1}$ for water, 1740 $cm.^{-1}$ for α-pyrone carbonyl group and 1355 $cm.^{-1}$ for geminal dimethyl group.

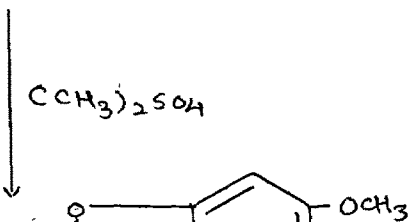


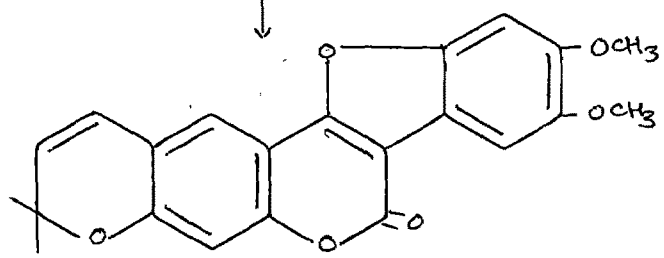
LII LIII





LIV





LI

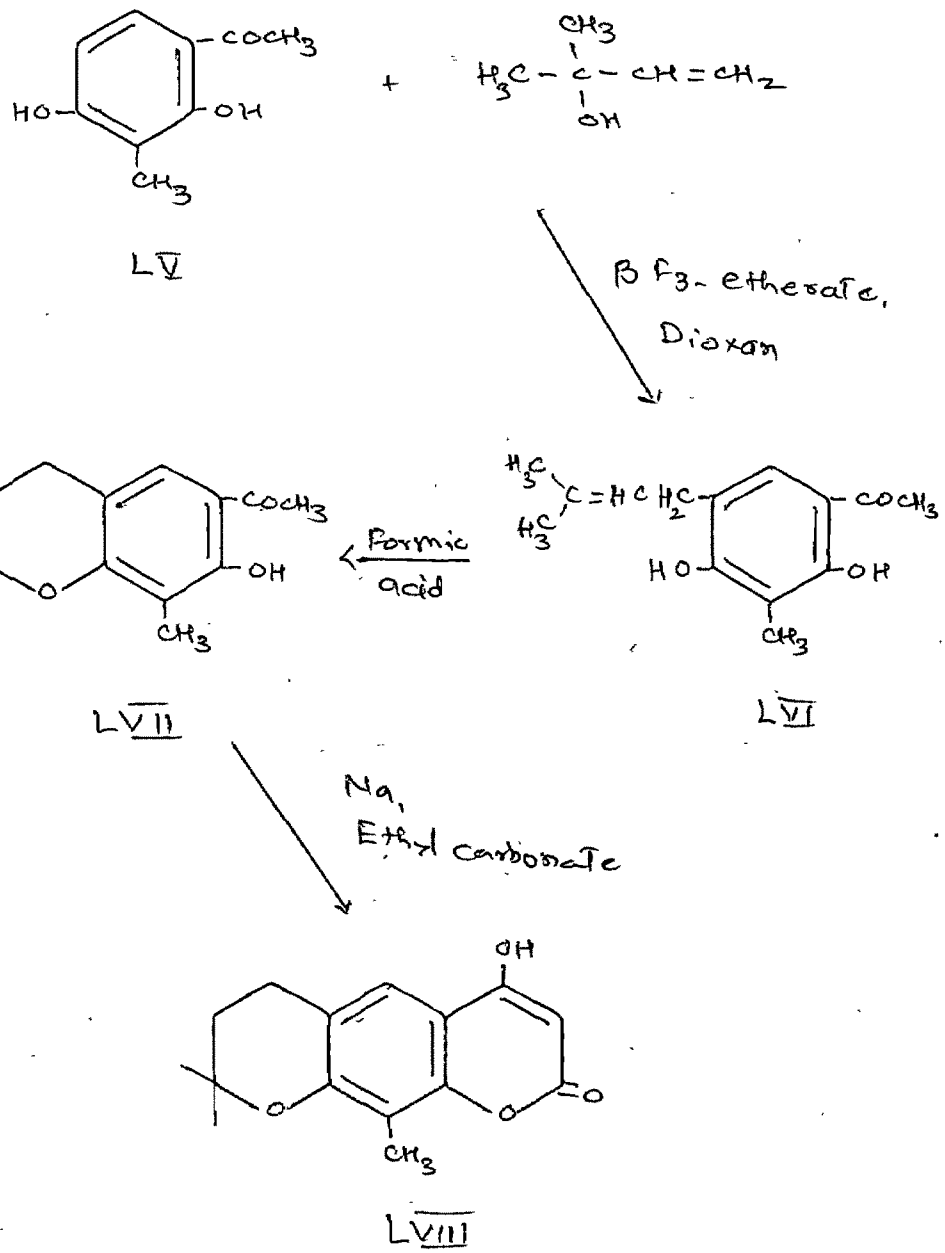
Synthesis of 8,9-dimethoxy-2,2,13-trimethyl--pyrano(3,2-g)coumestan

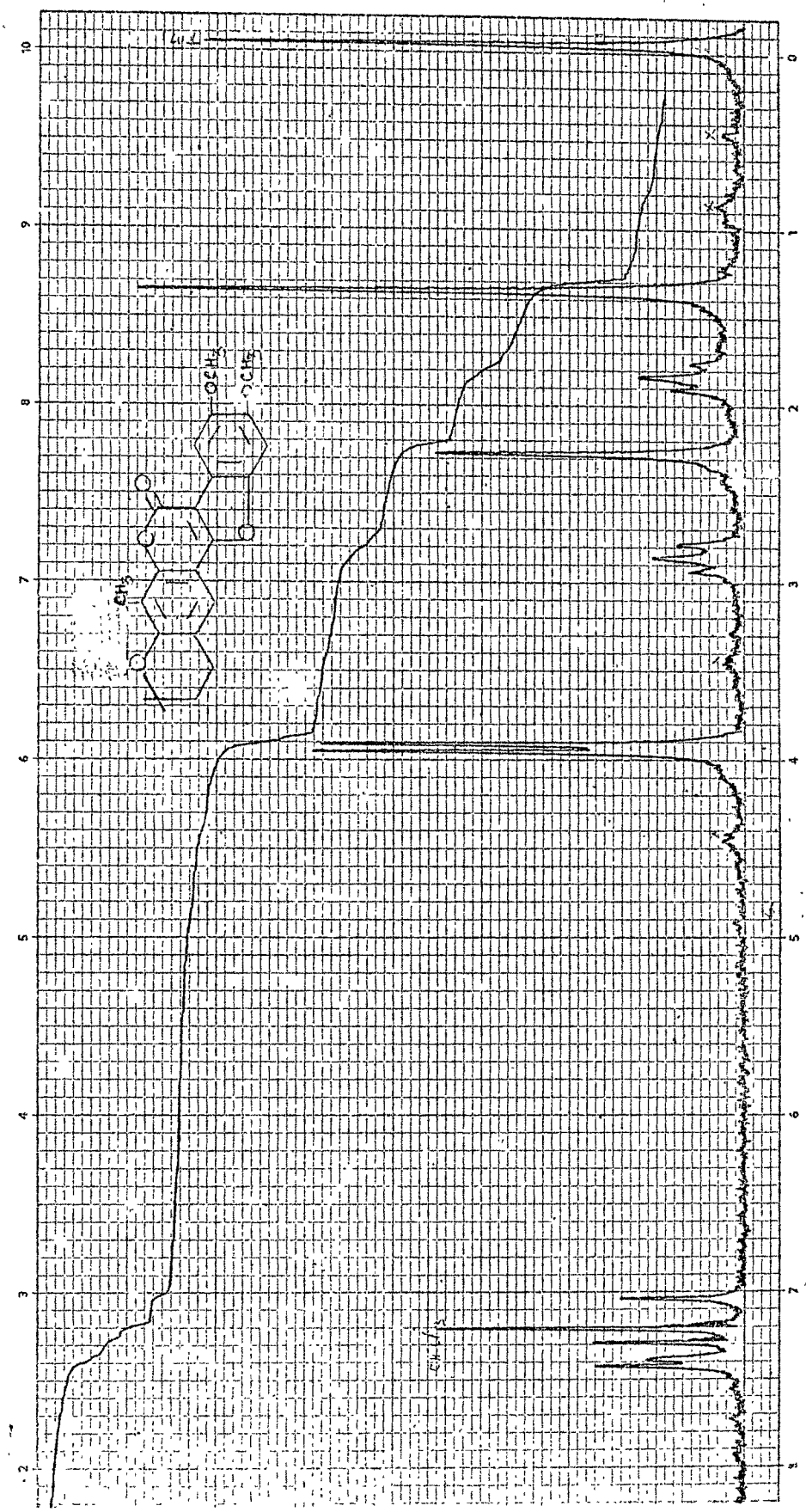
2,4-Dihydroxy-3-methylacetophenone (LV) when condensed with 2-methyl-but-3-en-2-ol in the presence of BF_3-etherate gave 2,4-dihydroxy-3-methyl-5-prenylacetophenone (LVI). The IR spectrum showed a broad band at 3280 $cm.^{-1}$ for hydroxyl groups, a band at 1630 $cm.^{-1}$ for a carbonyl group and a band at 1350 $cm.^{-1}$ for a geminal dimethyl group. This, (LVI), was converted to 3,4-dihydro-6-acetyl-7-hydroxy-2,2,8-trimethylchromene (LVII) by heating it with formic acid on a steam bath. This was further reacted with diethylcarbonate in the presence of pulverised sodium to give 3,4-dihydro-6-hydroxy-8-oxo-8H-2,2,10-trimethylpyrano(3,2-g)benzopyran (LVIII). This on oxidative coupling with catechol in the presence of potassium iodate and sodium acetate gave 8,9-dihydroxy-3,4-dihydro-2,2,13-trimethylpyrano(3,2-g)coumestan (LIX), which was methylated with dimethyl sulphate to 8,9-dimethoxy-3,4-dihydro-2,2,13-trimethylpyrano(3,2-g)coumestan (LX). The IR spectrum showed the following bands :- 1740 $cm.^{-1}$ (α-pyrone carbonyl group), 1360 $cm.^{-1}$ (geminal dimethyl group) and 1280 $cm.^{-1}$ (aromatic ether linkage).

The NMR spectrum of (LX) showed the following signals :-

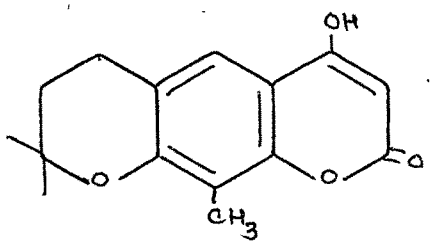
δ 1.35, singlet, geminal dimethyl group at position-2; 1.85, and 2.87, two triplets, J=7Hz, two methylene groups

at positions-3 and -4; 2.08, singlet, methyl group at position-13; 3.90 and 3.95, two singlets, two methoxy groups at positions-8 and -9; 7.04, singlet, one proton aromatic at position-5 and 7.30 and 7.41, two singlets, two protons aromatic, at positions-7 and -10 (Fig.2).



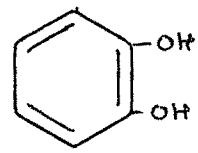


(Fig. 2) : 8,9-Dimethoxy-3,4-dihydro-2,2,13-trimethylpyrano(3,2-g)coumestan

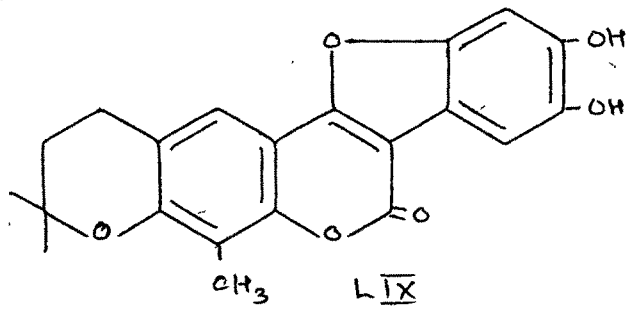


LVIII

+

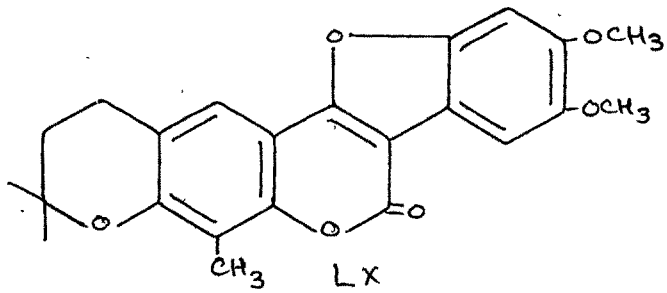


KIO_3
NaOAc



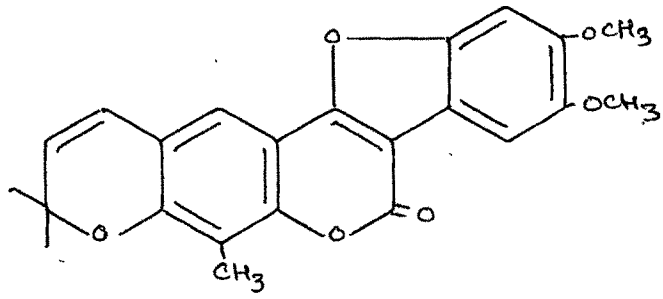
LIX

$(CH_3)_2SO_4$



LX

DDQ or
Pd/c



LXI

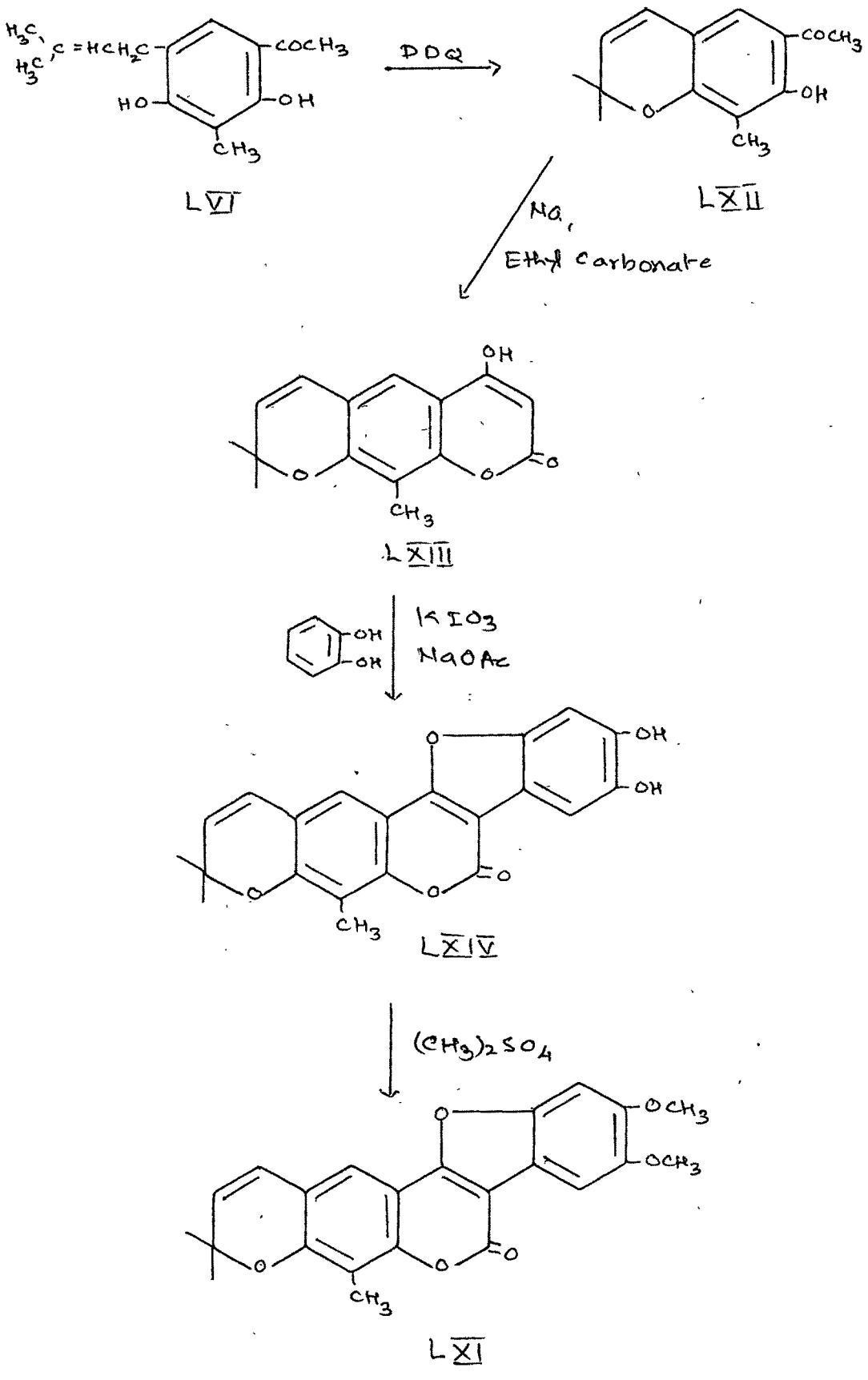
Dehydrogenation of (LX) failed to give 8,9-dimethoxy-2,2,13-trimethylpyrano(3,2-g)coumestan (LXI). The following alternative route was then adopted to synthesise (LXI).

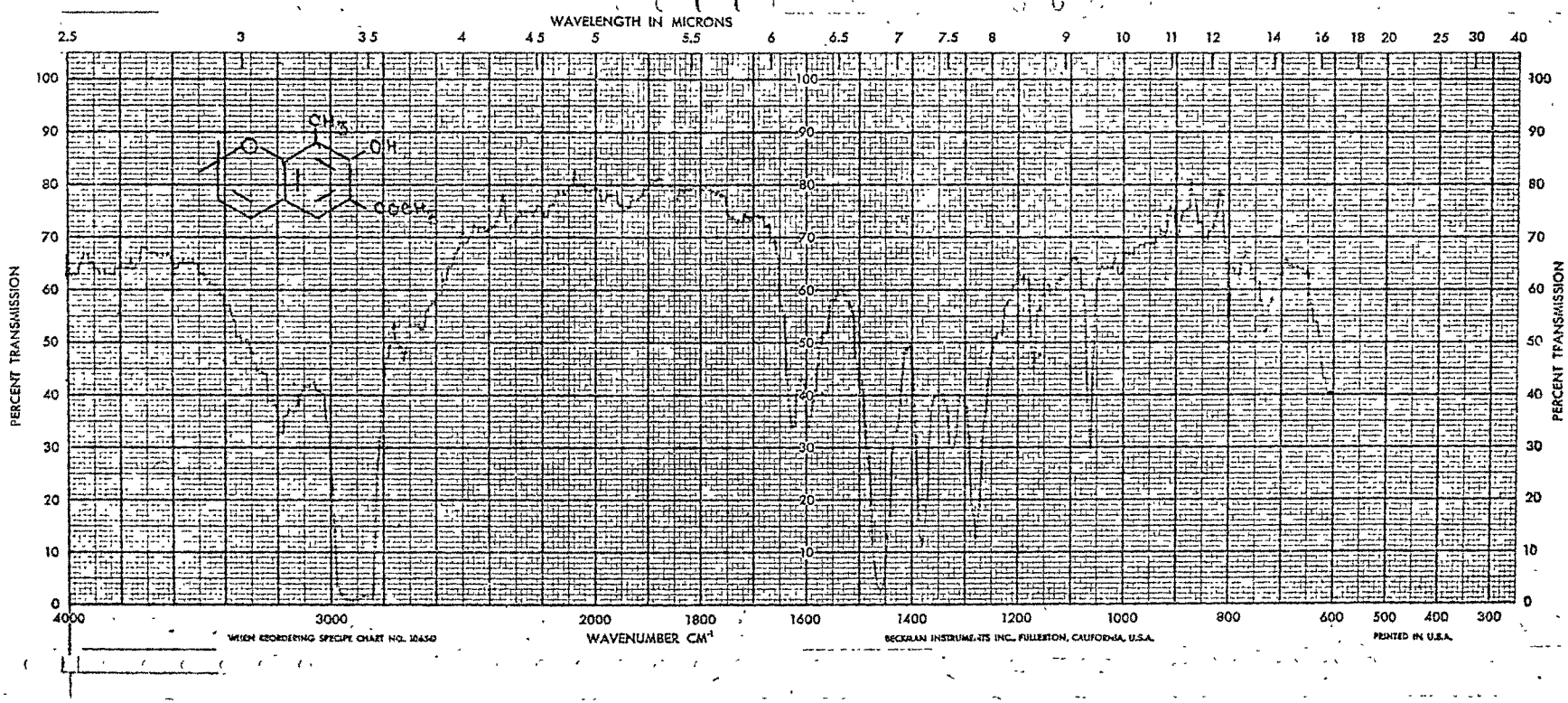
2,4-Dihydroxy-3-methyl-5-prenylacetophenone (LVI) on refluxing with DDQ in dry benzene yielded 6-acetyl-7-hydroxy-2,2,8-trimethylchromene (LXII). The structure was confirmed by its IR and NMR spectra :-

IR (nujol) : 3200 $cm.^{-1}$ (hydroxyl group), 1630 $cm.^{-1}$ (carbonyl group) and 1370 $cm.^{-1}$ (geminal dimethyl group).(Fig.3)

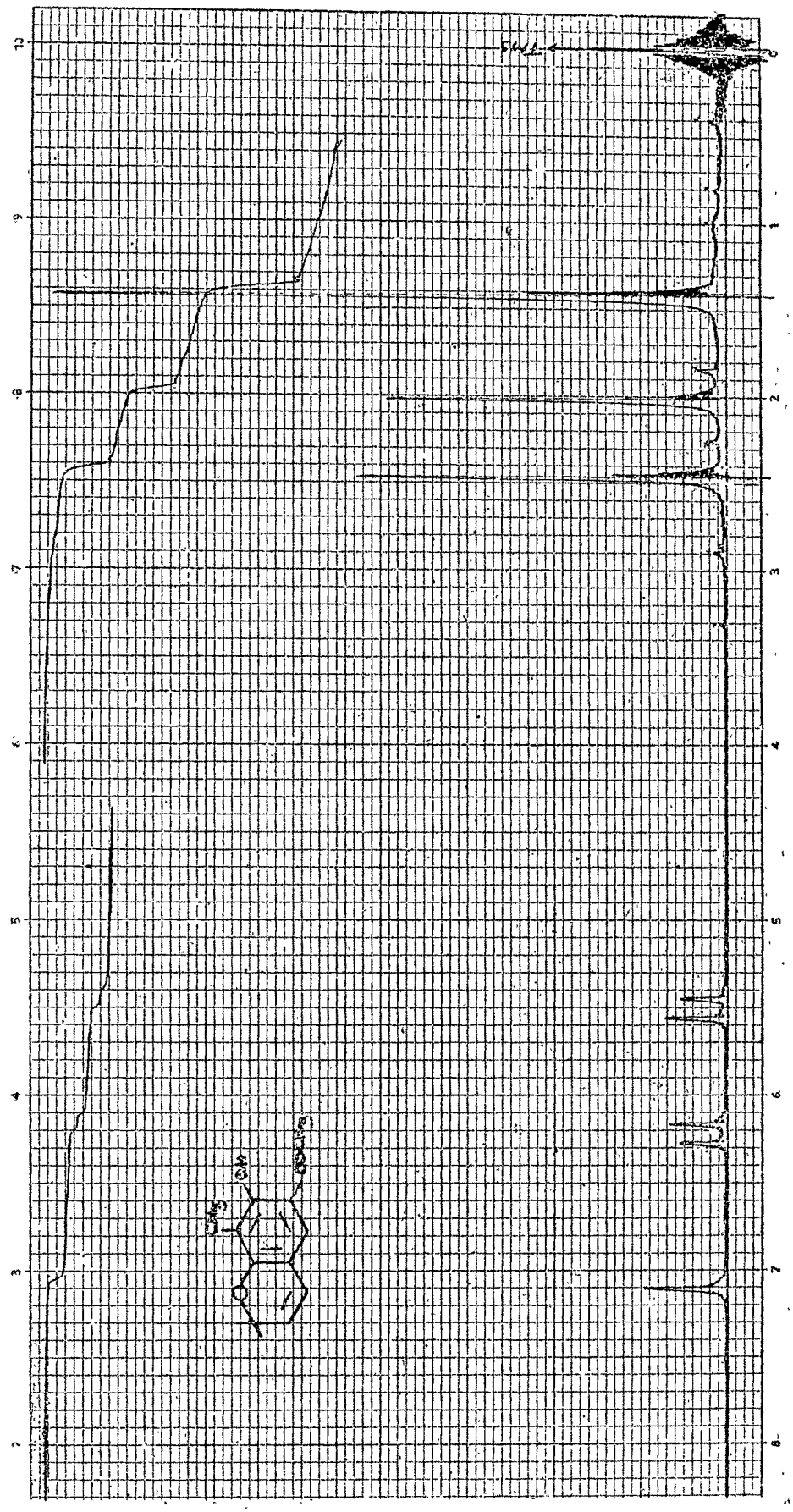
NMR (CCl_4) : δ 1.42, singlet, geminal dimethyl group at position-2; 2.02, singlet, methyl group of $-COCH_3$ at position-6; 2.48, singlet, methyl group of at position-8; 5.50 and 6.24, two doublets, J=9Hz, two protons at positions -3 and -4 and 7.10, singlet, one proton aromatic. (Fig.4)

(LXII) on treatment with diethyl carbonate in the presence of pulversied sodium gave 6-hydroxy-8-oxo-8H-2,2,10-trimethylpyrano(3,2-g)benzopyran (LXIII). This on oxidative coupling with catechol in the presence of potassium iodate and sodium acetate gave 8,9-dihydroxy-2,2,13-trimethylpyrano-(3,2-g)coumestan (LXIV) which on methylation with dimethyl sulphate gave 8,9-dimethoxy-2,2,13-trimethylpyrano(3,2-g)-coumestan (LXI). The structure of (LXI) was confirmed by its IR and NMR spectra.


DDQ
LVI
LXII
Na,
Ethyl carbonate
LXIII
KIO3
NaOAc
LXIV
(CH3)2SO4
LXI



(Fig. 3) : 6-Acetyl-7-hydroxy-2,2,8-trimethylchromene



(Fig. 4) : 6-Acetyl-7-hydroxy-2,2,8-trimethylchromene

IR (nujol) : 1735 $cm.^{-1}$ (α-pyrone carbonyl group stretching frequency), 1365 $cm.^{-1}$ (geminal dimethyl group stretching frequency) and 1278 $cm.^{-1}$ (aromatic ether linkage).

NMR ($CDCl_3$) : δ 1.50, singlet, geminal dimethyl group at position-2; 2.35, singlet, methyl group at position -13; 3.92 and 3.98, two singlets, two methoxy groups at positions-8 and -9; 5.70 and 6.40, two doublets, J=9Hz, two protons at positions-3 and -4 and 7.00-7.80, multiplet, three protons aromatic at positions-5, -7 and -10.

EXPERIMENTAL

8,9-Dimethoxy-2,2-dimethylpyrano(2,3-h)coumestan (XLIII) : 2,2-Dimethyl-3,4-dihydro-8-hydroxy-6-oxo-6H-pyrano(2,3-h)-benzopyran (XL) :

3,4-Dihydro-6-acetyl-5-hydroxy-2,2-dimethylchromene was prepared according to Seshadri et al.[47]

A mixture of 3,4-dihydro-6-acetyl-5-hydroxy-2,2-dimethylchromene (2.0 g.), diethyl carbonate (10 ml.) and pulverised sodium (2.0 g.) was heated on a water bath for 16 hr. After completion of the reaction, alcohol (10 ml.) was added to decompose the unreacted sodium and then the mixture was added to ice-cold water. The solution was then extracted with ether and the aqueous layer was acidified. The separated product was filtered and again treated with sodium bicarbonate solution. The sodium bicarbonate soluble fraction on acidification gave a solid, 2,2-dimethyl-3,4-dihydro-8-hydroxy-6-oxo-6H-pyrano(2,3-h)benzopyran, crystallised from dilute alcohol, m.p. 172°. Yield 0.8 g.

Analysis : Found : C, 64.21 ; H, 5.72 %

$C_{14}H_{14}O_4.H_2O$ requires : C, 63.63 ; H, 6.06 %.

8,9-Dihydroxy-2,2-dimethyl-3,4-dihydropyrano(2,3-h)-coumestan (XLI) :

Catechol (0.11 g.) was added to a solution of 2,2-dimethyl-3,4-dihydro-8-hydroxy-6-oxo-6H-pyrano(2,3-h)-

-benzopyran (0.23 g.) and sodium acetate (0.25 g.) in aqueous acetone (1:1 ; 25 ml.). To this solution, aqueous solution of potassium iodate (0.65 g.) and sodium acetate (0.25 g.) was added dropwise with constant stirring. After 15 minutes the separated product was filtered, washed with water several times and dried. The product 8,9-dihydro-2,2-dimethyl-3,4-dihydropyrano(2,3-h)coumestan could not be crystallised, but it gave green colouration with alcoholic ferric chloride solution. M.p. above 300°. It was then directly methylated.

8,9-Dimethoxy-2,2-dimethyl-3,4-dihydropyrano(2,3-h)-coumestan (XLII) :

A mixture of 8,9-dihydroxy-2,2-dimethyl-3,4-dihydropyrano(2,3-h)coumestan (0.3 g.), dimethyl sulphate (0.25 g.), dry acetone (100 ml.) and anhydrous potassium carbonate (1.5 g.) was refluxed on a water bath for 6 hr. On evaporation of acetone the separated product was filtered, washed with dilute sodium hydroxide solution and crystallised from benzene-petroleum ether mixture, m.p. 207-8°. Yield 0.3 g.

Analysis : Found : C, 68.99 ; H, 5.21 %.

$C_{22}H_{20}O_6$ requires : C, 69.47 ; H, 5.26 %.

2,2-Dimethyl-8-hydroxy-6-oxo-6H-pyrano(2,3-h)benzopyran (XLIV) :

2,2-Dimethyl-6-acetyl-5-hydroxychromene (1.0 g.) was condensed with diethyl carbonate (6 ml.) and pulverised sodium (1.0 g.) on a water bath for 16 hr. at 60-70°. After completion of the reaction, the alcohol (10 ml.) was added

to decompose the unreacted sodium and then the mixture was added to ice-cold water. The solution was then extracted with ether and the aqueous layer on acidification gave a solid, which was further dissolved in sodium bicarbonate solution. The sodium bicarbonate soluble fraction on acidification gave a solid, 2,2-dimethyl-8-hydroxy-6-oxo-6H-pyrano--(2,3-h)benzopyran, crystallised from dilute alcohol. This was further methylated to its methylether by refluxing with dimethyl sulphate in the presence of anhydrous potassium carbonate in acetone. The solid, 2,2-dimethyl-8-methoxy-6--oxo-6H-pyrano(2,3-h)benzopyran, crystallised from benzene-petroleum ether mixture, m.p. 150°. Yield 0.5 g.

Analysis : Found : C, 69.85 ; H, 5.26 %

$C_{15}H_{14}O_4$ requires : C, 69.77 ; H, 5.42 %.

8,9-Dihydroxy-2,2-dimethylpyrano(2,3-h)coumestan (XLVI) :

Catechol (0.11 g.) was added to a solution of 2,2-dimethyl-8-hydroxy-6-oxo-6H-pyrano(2,3-h)benzopyran (0.25 g.) and sodium acetate (0.25 g.) in aqueous acetone (1:1 ; 25 ml.). To this, a solution of potassium iodate (0.65 g.) and sodium acetate (0.25 g.) was added slowly with constant stirring. The product separated after 15 minutes was filtered, washed with water and dried. The product was directed methylated to its methylether. It gave green colouration with alcoholic ferric chloride solution. M.p. above 300°.

8,9-Dimethoxy-2,2-dimethylpyrano(2,3-h)coumestan (XLIII) :

A mixture of 8,9-dihydroxy-2,2-dimethylpyrano-(2,3-h)coumestan (0.3 g.), dimethyl sulphate (0.25 g.), dry acetone (100 ml.) and anhydrous potassium carbonate (1.5 g.) was refluxed on a water bath for 6 hr. The solid separated after evaporation of acetone was filtered, washed with dilute sodium hydroxide solution and crystallised from benzene-petroleum ether mixture, m.p. 214°. Yield 0.25 g.

Analysis : Found : C, 67.95 ; H, 4.79 %

$C_{22}H_{18}O_6.1/2\ H_2O$ requires : C, 68.24 ; H, 4.94 %.

8,9-Dimethoxy-2,2-dimethylpyrano(3,2-g)coumestan (LI) :

2,2-Dimethyl-3,4-dihydro-6-hydroxy-8-oxo-8H-pyrano(3,2-g)-benzopyran (XLVIII) :

A mixture of 3,4-dihydro-6-acetyl-7-hydroxy-2,2-dimethylchromene (2.0 g.), diethyl carbonate (10 ml.) and pulverised sodium (2.0 g.) was heated on a water bath for 16 hr. After completion of the reaction it was worked out as before. The solid, 2,2-dimethyl-3,4-dihydro-6-hydroxy-8-oxo-8H-pyrano(3,2-g)benzopyran, obtained after acidification of sodium bicarbonate filtrate, was crystallised from aqueous alcohol, m.p. 138°. Yield 0.6 g.

Analysis : Found : C, 64.55 ; H, 5.79 %

$C_{14}H_{14}O_4.H_2O$ requires : C, 63.63 ; H, 6.06 %.

The methoxy derivative of the above coumarin was prepared by refluxing it (0.2 g.) with dimethyl sulphate (0.2 ml.)

and anhydrous potassium carbonate (1.0 g.) in acetone (25 ml.) for 3 hr. Water was added to the solution and the solid, 2,2-dimethyl-3,4-dihydro-6-methoxy-8-oxo-8H-pyrano(3,2-g)benzopyran, separated was filtered and crystallised from benzene-petroleum ether mixture, m.p. 218-20°. Yield 0.1 g.

Analysis : Found : C, 68.74 ; H, 5.93 %

$C_{15}H_{16}O_4$ requires : C, 69.23 ; H, 6.15 %.

8,9-Dihydroxy-2,2-dimethyl-3,4-dihydropyrano(3,2-g)coumestan (XLIX) :

Catechol(0.11 g.) was added to a solution of 2,2-dimethyl-3,4-dihydro-6-hydroxy-8-oxo-8H-pyrano(3,2-g)benzopyran (0.3 g.) and sodium acetate (0.25 g.) in aqueous acetone (1:1 ; 25 ml.). To this solution, aqueous solution of potassium iodate (0.65 g.) and sodium acetate (0.25 g.) was added dropwise with constant stirring. The stirring was continued for 15 minutes and the product separated was filtered, washed and dried. It gave green colouration with alcoholic ferric chloride solution. M.p. above 300°. The product was directly methylated to its methylether.

8,9-Dimethoxy-2,2-dimethyl-3,4-dihydropyrano(3,2-g)coumestan (L) :

A mixture of 8,9-dihydroxy-2,2-dimethyl-3,4-dihydropyrano(3,2-g)coumestan (0.3 g.), dimethyl sulphate (0.25 g.), dry acetone (100 ml.) and anhydrous potassium carbonate (1.5 g.) was refluxed on a water bath for 6 hr. Acetone was evaporated and the solid, 8,9-dimethoxy-2,2-di-

-methyl-3,4-dihydropyrano(3,2-g)coumestan, separated was filtered, washed with dilute sodium hydroxide solution and crystallised from benzene-petroleum ether mixture, m.p. 234-35°. Yield 0.3 g.

Analysis : Found : C, 69.71 ; H, 5.45 %;

$C_{22}H_{20}O_6$ requires : C, 69.47 ; H, 5.26 %.

2,2-Dimethyl-6-hydroxy-8-oxo-8H-pyrano(3,2-g)benzopyran (LIII) :

2,2-Dimethyl-7-hydroxy-6-acetylchromene (2.0 g.) was heated with diethyl carbonate (10 ml.) in the presence of pulverised sodium (2.0 g.) on a water bath for 6 hr. Alcohol was added to the reaction mixture to destroy the unreacted sodium and diethyl carbonate was removed by ether. The alkaline solution was acidified and the solid obtained was crystallised from alcohol. The product, 2,2-dimethyl-6-hydroxy-8-oxo-8H-pyrano(3,2-g)benzopyran, was soluble in sodium bicarbonate solution. As the analysis of this compound did not agree with the molecular formula, its methylether was prepared by methylating it (0.2 g.) with dimethyl sulphate (0.2 ml.) in the presence of anhydrous potassium carbonate (1.0 g.) in acetone (20 ml.) and the mixture was refluxed for 3 hr. The product 2,2-dimethyl-6-methoxy-8-oxo-8H-pyrano-(3,2-g)benzopyran, obtained was crystallised from benzene-petroleum ether mixture, m.p. 185°. Yield 0.15 g.

Analysis : Found : C, 69.49 ; H, 5.88 %

$C_{15}H_{14}O_4$ requires : C, 69.77 ; H, 5.42 %.

2,2-Dimethyl-6-methoxy-8-oxo-8H-pyrano(3,2-g)-benzopyran was also obtained by refluxing 2,2-dimethyl-3,4-dihydro-6-methoxy-8-oxo-8H-pyrano(3,2-g)benzopyran (0.5 g.) with DDQ (0.5 g.) in dry benzene (10 ml.) for 70 hr. on a water bath. The solid separated during the refluxion was filtered hot and the filtrate on concentration followed by column chromatography over silica gel gave 2,2-dimethyl-6-methoxy-8-oxo-8H-pyrano(3,2-g)benzopyran, m.p. 185-86°. Yield 0.3 g.

The mixed m.p. with the product obtained by the above method did not depress.

8,9-Dihydroxy-2,2-dimethylpyrano(3,2-g)coumestan (LIV) :

Catechol (0.11 g.) was added to a solution of 2,2-dimethyl-6-hydroxy-8-oxo-8H-pyrano(3,2-g)benzopyran (0.3 g.) and sodium acetate (0.25 g.) in aqueous acetone (1:1 ; 25 ml.). To this, solution of potassium iodate (0.65 g.) and sodium acetate (0.25 g.) was added slowly with constant stirring. The product separated was filtered, washed with water and dried. M.p. above 300°. It gave green colouration with alcoholic ferric chloride solution.

8,9-Dimethoxy-2,2-dimethylpyrano(3,2-g)coumestan (LI) :

A mixture of 8,9-dihydroxy-2,2-dimethylpyrano-(3,2-g)coumestan (0.2 g.), dimethyl sulphate (0.25 ml.), dry acetone (100 ml.) and potassium carbonate (1.5 g.) was refluxed on a water bath for 6 hr. The product, after evaporation of acetone, was filtered, washed with dilute

sodium hydroxide solution and then crystallised from benzene-petroleum ether mixture to give 8,9-dimethoxy-2,2-dimethylpyrano(3,2-g)coumestan, m.p. 140-42°. Yield 0.2 g.

Analysis : Found : C, 68.64 ; H, 5.32 %

$C_{22}H_{18}O_6.1/2\ H_2O$ requires : C, 68.24 ; H, 4.94 %.

8,9-Dimethoxy-2,2,13-trimethylpyrano(3,2-g)coumestan (LXI) :

2,4-Dihydroxy-3-methyl-5-prenylacetophenone (LVI) :

To a stirred solution of 2,4-dihydroxy-3-methylacetophenone (1.2 g.) in dry dioxan (10 ml.) was added a solution of 2-methyl-but-3-en-2-ol (0.6 g.) in dioxan (5 ml.) in the presence of BF_3-etherate (0.5 ml.) and the whole solution was stirred for 1 hr. at room temperature. The solution was then diluted with ether and the ether layer was washed with water (3x100 ml.) to discharge the colour. The solution was then washed with sodium carbonate solution (10 %; 3x100 ml.) which on acidification gave unreacted 2,4-dihydroxy--3-methylacetophenone (0.5 g.). The ethereal layer on examination by TLC (chloroform) showed the presence of two compounds. This was then subjected to the column chromatography over silica gel and the column successively eluted with (i) benzene-petroleum ether (80:20) and (ii) benzene-ethyl acetate (80:20). Fraction (i) gave a solid 2,4-dihydroxy-3-methyl-5--prenylacetophenone, crystallised from benzene-petroleum ether mixture, m.p. 117-18°. Yield 0.4 g. Fraction (ii) gave the original ketone, m.p. 150-51°.

IR (nujol) : 3280 $cm.^{-1}$ (hydroxyl group), 1630 $cm.^{-1}$ (carbonyl stretching frequency) and 1350 $cm.^{-1}$ (geminal dimethyl group stretching frequency).

NMR (CCl_4) : δ 1.80 and 1.82, two singlets, geminal dimethyl group; 2.10, singlet, methyl group at position -1 of $COCH_3$; 2.52, singlet, methyl group at position-3; 3.30, doublet, two protons of $-\underline{CH_2}=CH$; 5.30, triplet, one proton of $-CH_2=\underline{CH}$; 5.60, singlet, one proton of -OH group and 7.25, singlet, one proton aromatic at position-6.

Analysis : Found : C, 70.89 ; H, 7.45 %

$C_{14}H_{18}O_3$ requires : C, 70.59 ; H, 7.56 %.

3,4-Dihydro-2,2,8-trimethyl-7-hydroxy-6-acetylchromene (LVII) :

2,4-Dihydroxy-3-methyl-5-prenylacetophenone (1.0 g.) was heated on a steam bath with formic acid (10 ml.) for 1 1/2 hr. The solution was then poured into the water and the solid was filtered, washed with water and crystallised from petroleum ether to give 3,4-dihydro-2,2,8-trimethyl-7-hydroxy--6-acetylchromene in white plates, m.p. 112°. Yield 0.8 g.

IR (nujol) : 3260 $cm.^{-1}$ (hydroxyl group), 1730 $cm.^{-1}$ (carbonyl stretching frequency) and 1370 $cm.^{-1}$ (geminal dimethyl group stretching frequency).

NMR (CCl_4) : δ 1.35, singlet, geminal dimethyl group at position-2; 2.00, singlet, methyl group of $COCH_3$ at position-6; 2.45, singlet, methyl group at position-8; 1.80 and 2.73, two triplets, J=8Hz, two methylene groups at

positions-3 and -4 and 7.20, singlet, one proton aromatic at position-5.

Analysis : Found : C, 70.80 ; H, 7.64 %

$C_{14}H_{18}O_3$ requires : C, 70.59 ; H, 7.56 %.

3,4-Dihydro-6-hydroxy-8-oxo-8H-2,2,10-trimethylpyrano(3,2-g)--benzopyran (LVIII) :

A mixture of 3,4-dihydro-7-hydroxy-2,2,8-trimethyl--6-acetylchromene (2.0 g.), diethyl carbonate (10 ml.) and pulverised sodium (2.0 g.) was heated on a water bath for 16 hr. Alcohol was added to the reaction mixture to destroy the the unreacted sodium and diethyl carbonate was removed by ether. The alkaline solution on acidification, gave a solid, 3,4-dihydro-6-hydroxy-8-oxo-8H-2,2,10-trimethylpyrano(3,2-g)-benzopyran, crystallised from aqueous alcohol, m.p. 191-93°. Yield 01.0 g.

This coumarin (0.2 g.) was refluxed with dimethyl sulphate (0.2 g.) and anhydrous potassium carbonate (1.0 g.) in dry acetone (10 ml.) for 3 hr. on a water bath. The solvent was removed and water was added to the residue. The solid separated was filtered, and crystallised from benzene-petroleum ether mixture to give 3,4-dihydro-6-methoxy-8-oxo--8H-2,2,10-trimethylpyrano(3,2-g)benzopyran, m.p. 178-80°.

Analysis : Found : C, 70.45 ; H, 6.67 %

$C_{16}H_{18}O_4$ requires : C, 70.07 ; H, 6.56 %.

8,9-Dihydroxy-2,2,13-trimethyl-3,4-dihydropyrano(3,2-g)-coumestan (LIX) :

Catechol (0.11 g.) was added to a solution of 3,4-dihydro-6-hydroxy-8-oxo-8H-2,2,10-trimethylpyrano(3,2-g)-benzopyran (0.3 g.) and sodium acetate (0.25 g.) in aqueous acetone (1:1 ; 25 ml.). To this, aqueous solution of potassium iodate (0.65 g.) and sodium acetate (0.25 g.) was added dropwise with constant stirring. After 15 minutes the solid, 8,9-dihydroxy-2,2,13-trimethyl-3,4-dihydropyrano(3,2-g)-coumestan, separated was filtered, washed with water and dried. It gave green colouration with alcoholic ferric chloride solution and it could not be crystallised from any organic solvent, so was directly methylated to its methyl-ether.

8,9-Dimethoxy-2,2,13-trimethyl-3,4-dihydropyrano(3,2-g)-coumestan (LX) :

A mixture of 8,9-dihydroxy-2,2,13-trimethyl-3,4-dihydropyrano(3,2-g)coumestan (0.2 g.), dimethyl sulphate (0.25 g.), dry acetone (100 ml.) and anhydrous potassium carbonate (1.5 g.) was refluxed on a water bath for 6 hr. After evaporation of the solvent, the solid separated was filtered, washed with dilute solution of sodium hydroxide and crystallised from benzene-petroleum ether mixture, to give 8,9-dimethoxy-2,2,13-trimethyl-3,4-dihydropyrano(3,2-g)-coumestan, m.p. 232-33°. Yield 0.15 g.

Analysis : Found : C, 69.72 ; H, 5.97 %

$C_{23}H_{22}O_6$ requires : C, 70.07 ; H, 5.58 %.

2,2,8-Trimethyl-7-hydroxy-6-acetylchromene (LXII) :

To a solution of 2,4-dihydroxy-3-methyl-5-prenyl-acetophenone (0.2 g.) in dry benzene (10 ml.) was added DDQ (0.2 g.) and the solution heated on a boiling water bath for 15 minutes, when the solid hydroquinone derivative separated out, it was filtered hot, and the residue washed with benzene. The solvent was distilled off and the residue on chromatography on silica gel gave a solid, 2,2,8-trimethyl-7-hydroxy-6-acetyl--chromene, crystallised from petroleum ether, m.p. 81°. Yield 0.1 g.

Analysis : Found : C, 72.32 ; H, 6.68 %

$C_{14}H_{16}O_3$ requires : C, 72.41 ; H, 6.89 %.

6-Hydroxy-8-oxo-8H-2,2,10-trimethylpyrano(3,2-g)benzopyran (LXIII) :

2,2,8-Trimethyl-7-hydroxy-6-acetylchromene (2.0 g.) was condensed with diethyl carbonate (10 ml.) in the presence of pulverised sodium (2.0 g.) on heating in a water bath for 12 hr. Alcohol was added to the reaction mixture to destroy the unreacted sodium and diethyl carbonate was removed by ether. The alkaline solution, on acidification, gave 6-hydroxy--8-oxo-8H-2,2,10-trimethylpyrano(3,2-g)benzopyran , crystallised from aqueous alcohol, m.p. 210-12°. Yield 0.6 g.

This was directly refluxed with dimethyl sulphate (0.5 ml.) in the presence of anhydrous potassium carbonate (2.0 g.) in acetone (20 ml.). The solid obtained after working up the reaction, crystallised from benzene-petroleum ether mixture, to give 6-methoxy-8-oxo-8H-2,2,10-trimethyl-pyrano(3,2-g)benzopyran, m.p. 174-76°. Yield 0.5 g.

Analysis : Found : C, 71.04 ; H, 5.69 %

$C_{16}H_{16}O_4$ requires : C, 70.58 ; H, 5.88 %.

6-Methoxy-8-oxo-8H-2,2,10-trimethylpyrano(3,2-g)-benzopyran was also obtained by refluxing 3,4-dihydro-6--methoxy-8-oxo-8H-2,2,10-trimethylpyrano(3,2-g)benzopyran (0.5 g.) in dry benzene (20 ml.) with DDQ (0.5 g.) for 70 hr. and working up the reaction was carried out by filtering it hot and concentrating the filtrate. The solid obtained after chromatography over silica gel, crystallised from benzene-petroleum ether mixture, m.p. 175°. Yield 0.2 g.

The mixed m.p. of this compound did not depress with the compound prepared by the above method.

8,9-Dihydroxy-2,2,13-trimethylpyrano(3,2-g)coumestan (LXIV) :

Catechol (0.11 g.) was added to a solution of 6-hydroxy-8-oxo-8H-2,2,10-trimethylpyrano(3,2-g)benzopyran (0.2 g.) and sodium acetate (0.25 g.) in aqueous acetone (1:1 ; 25 ml.). To this, a solution of potassium iodate (0.65 g.) and sodium acetate (0.25 g.) was added dropwise with constant stirring. The solid separated after 15 minutes, was filtered,

washed with water and dried. 8,9-Dihydroxy-2,2,13-trimethyl--pyrano(3,2-g)coumestan, gave green colouration with alcoholic ferric chloride solution, m.p. above 300°. It was directly methylated to its methylether.

8,9-Dimethoxy-2,2,13-trimethylpyrano(3,2-g)coumestan (LXI) :

A mixture of 8,9-dihydroxy-2,2,13-trimethylpyrano--(3,2-g)coumestan (0.2 g.), dimethyl sulphate (0.25 g.), dry acetone (100 ml.) and anhydrous potassium carbonate (1.5 g.) was refluxed on a water bath for 6 hr. The residue after evaporation of solvent was diluted with water, filtered, washed with dilute sodium hydroxide solution and crystallised from benzene-petroleum ether mixture to give 8,9-dimethoxy--2,2,13-trimethylpyrano(3,2-g)coumestan, m.p. 220-222°. Yield 0.2 g.)

Analysis : Found : C, 68.66 ; H, 5.07 %

$C_{23}H_{20}O_6.1/2\ H_2O$ requires : C, 68.82 ; H, 5.27 %.

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CHAPTER II

SECTION II

SYNTHESIS OF FURANOCOUMARINS

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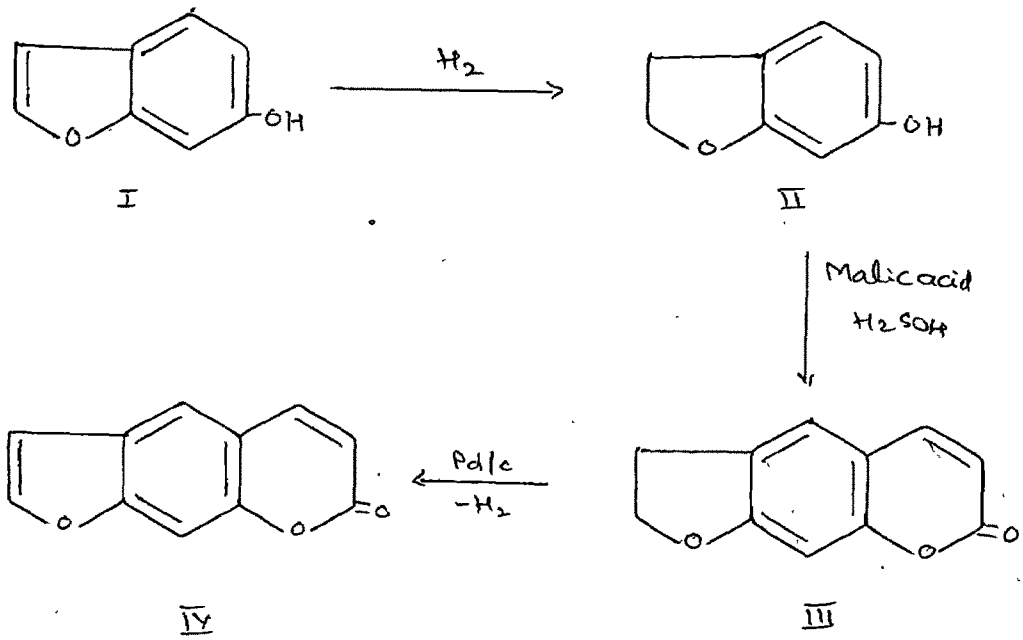
SYNTHESIS OF FURANOCOUMARINS

The review of the introductory furanocoumarins of other types, except types (F) and (G), being the matter of Chapter I is described therein. The methods for the synthesis of furanocoumarins of types (F) and (G) are as given below :-

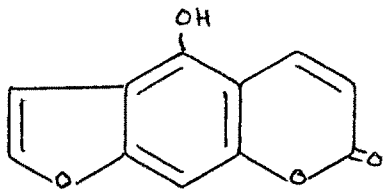
Psoralene or linear furanocoumarin of type (F), also known as ficusin, occurs in Ficus Carica Linn. and psoralea Corylifolia Linn. has been synthesised by Späth[1] from 6-hydroxybenzofuran (I) which was hydrogenated to



I II III IV

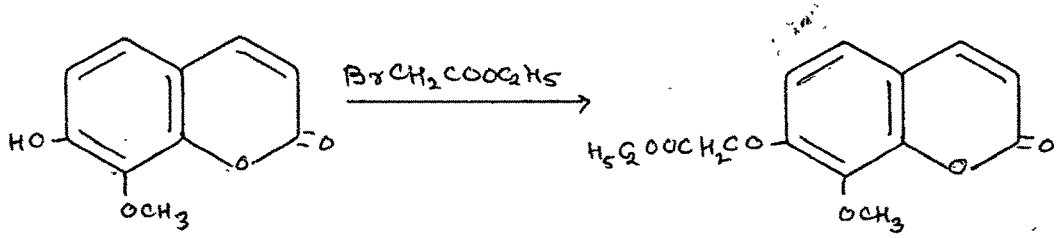
coumaran (II) followed by condensation with malic acid in the presence of sulphuric acid according to the von Pechmann procedure, giving 4',5'-dihydropsoralene (III), which on dehydrogenation gave psoralene (IV).

Later, Horning and Reisner[2] prepared different 5-substituted psoralenes. Bergaptol[3,4,5] (V) is of this type and was synthesised by Spath[6].

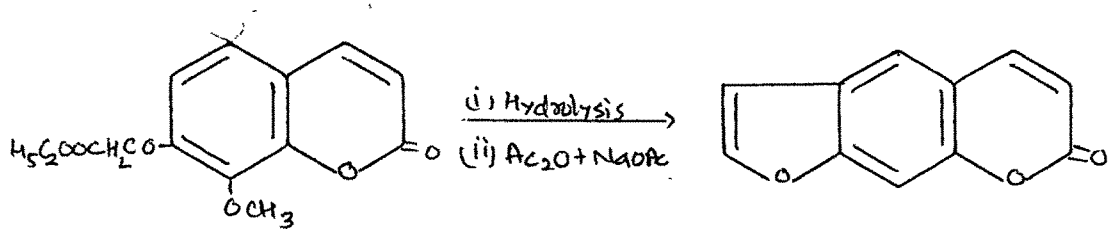


V

Xanthotoxin (VI) or 8-methoxypsoralene occurs in the seeds of Fagara xanthoxyloids Lam.[4,7] which was synthesised by Spath[8,9] and later by Rodighiero and Antonello[10] by first preparing 7-hydroxy-8-methoxy-6-formyl-coumarin (VII) and then treating it with ethylbromoacetate followed by hydrolysis, cyclisation and decarboxylation.



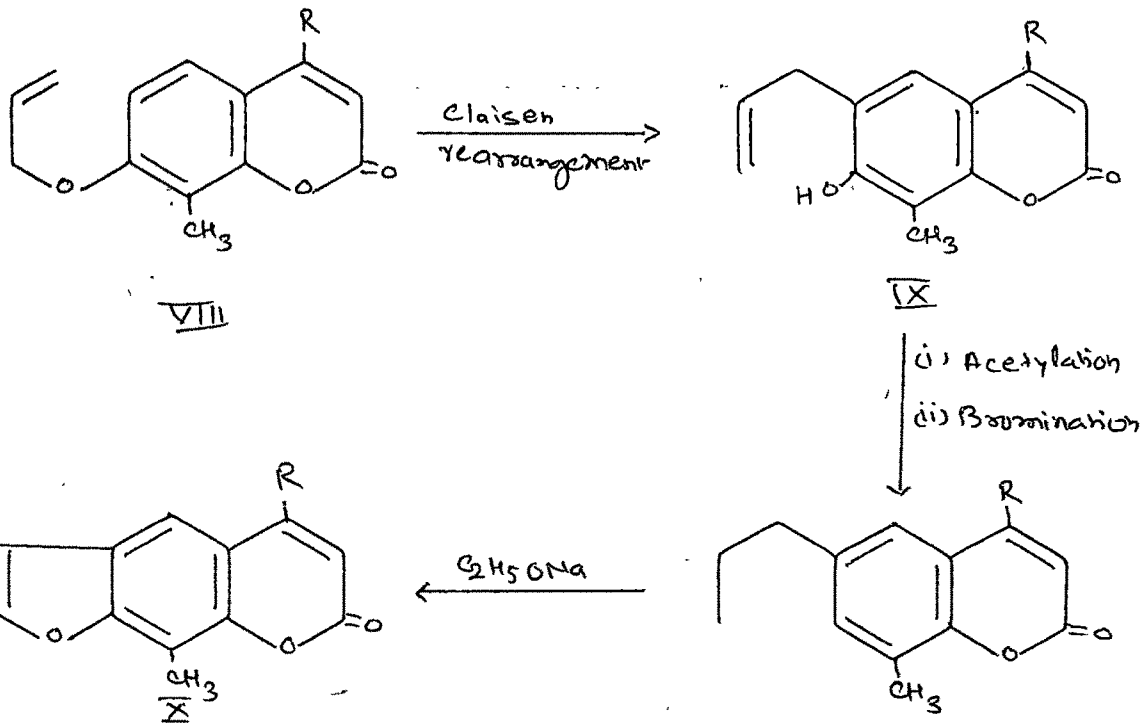
VII



VI

Ray, Silooja and Vaid[11] synthesised 3-methylpsoralene from umbelliferon. Limaye and Gangal[12] and Foster et al.[13] also synthesised some psoralene derivatives.

Kaufmann[14] prepared 4,5',8-trimethylpsoralene (Xa) and 5',8-dimethylpsoralene (Xb) by first carrying out Claisen migration of 7-allyloxy-4,8-dimethyl- (VIIIa) and 7-allyloxy-



VIII IX

X

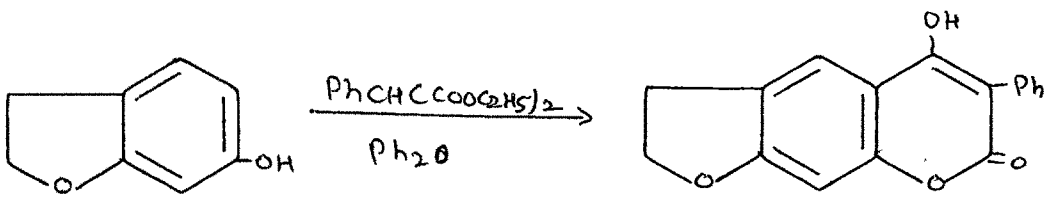
(a) R = CH_3 ; (b) R = H.

-8-methylcoumarin (VIIIb) to 7-hydroxy-6-allyl-4,8-dimethyl- (IXa) and 7-hydroxy-6-allyl-8-methylcoumarin (IXb), respectively. These were then acetylated, brominated and cyclised to obtain psoralene derivatives (Xa and Xb).

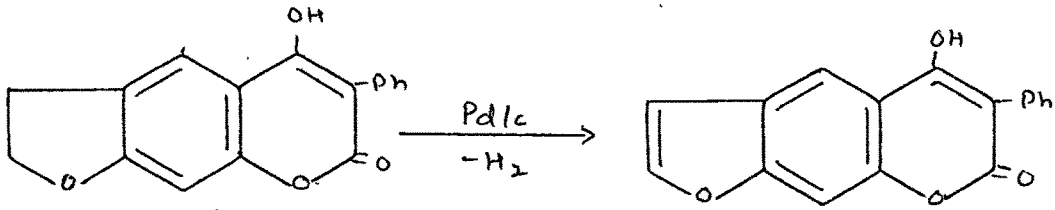
Using similar method Kaufmann synthesised 4,5'-dimethylpsoralene. Kaufmann and coworkers[15] synthesised psoralene derivatives having different substituents in 8-position using 8-aminopsoralene as an intermediate product.

Seshadri and coworkers[16] have obtained psoralene by ozonolysis of 6-dimethylallyl-7-hydroxycoumarin, followed by cyclisation of the aldehyde with o-phosphoric acid. Using the same method they have also synthesised xanthotoxin (VI).

Goudou and Blanchecotte[17] have condensed 6-hydroxycoumaran and phenyldiethylmalonic ester in diphenylether and obtained 4',5'-dihydro-4-hydroxy-3-phenylfurano-2',3',6,7-coumarin (XI) which was then dehydrogenated over palladised charcoal to give 4-hydroxy-3-phenylpsoralene (XII).

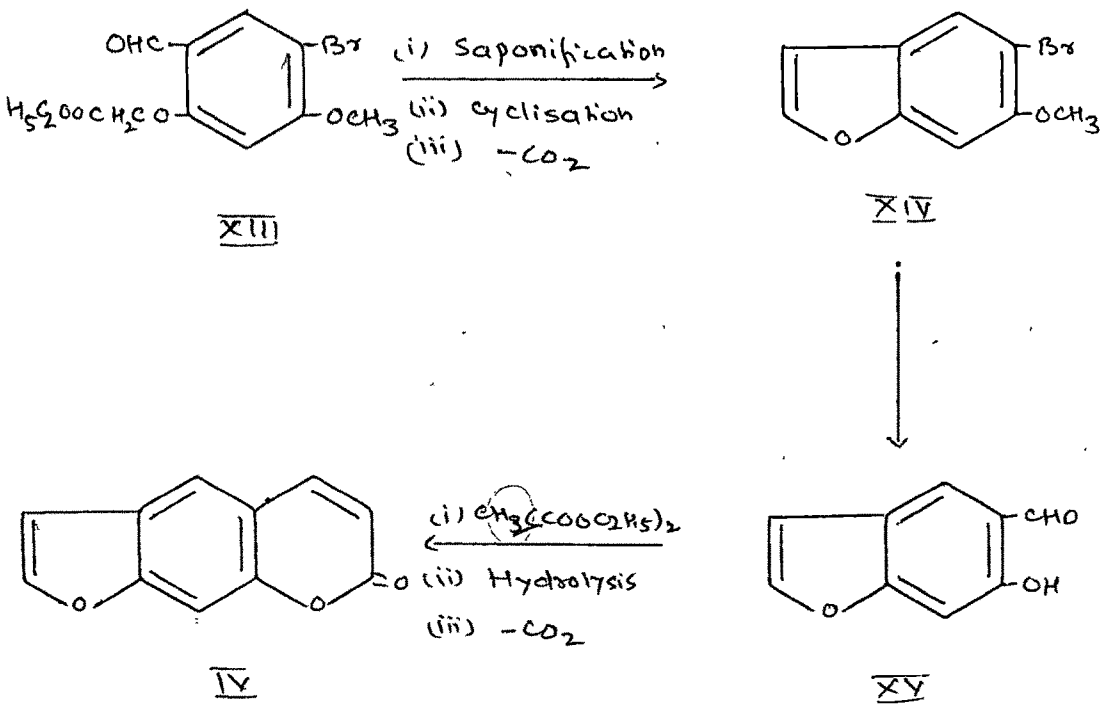


XI



XI XII

Kaufmann and coworkers[18] have developed a new synthetic route to synthesise psoralene. Bromination of ethyl(2-formyl-5-methoxyphenoxy)acetate gave the 4-bromo derivative (XIII) which was saponified and simultaneously cyclised and decarboxylated to 5-bromo-6-methoxybenzofuran (XIV). Lithium bromide interchange and then formylation and

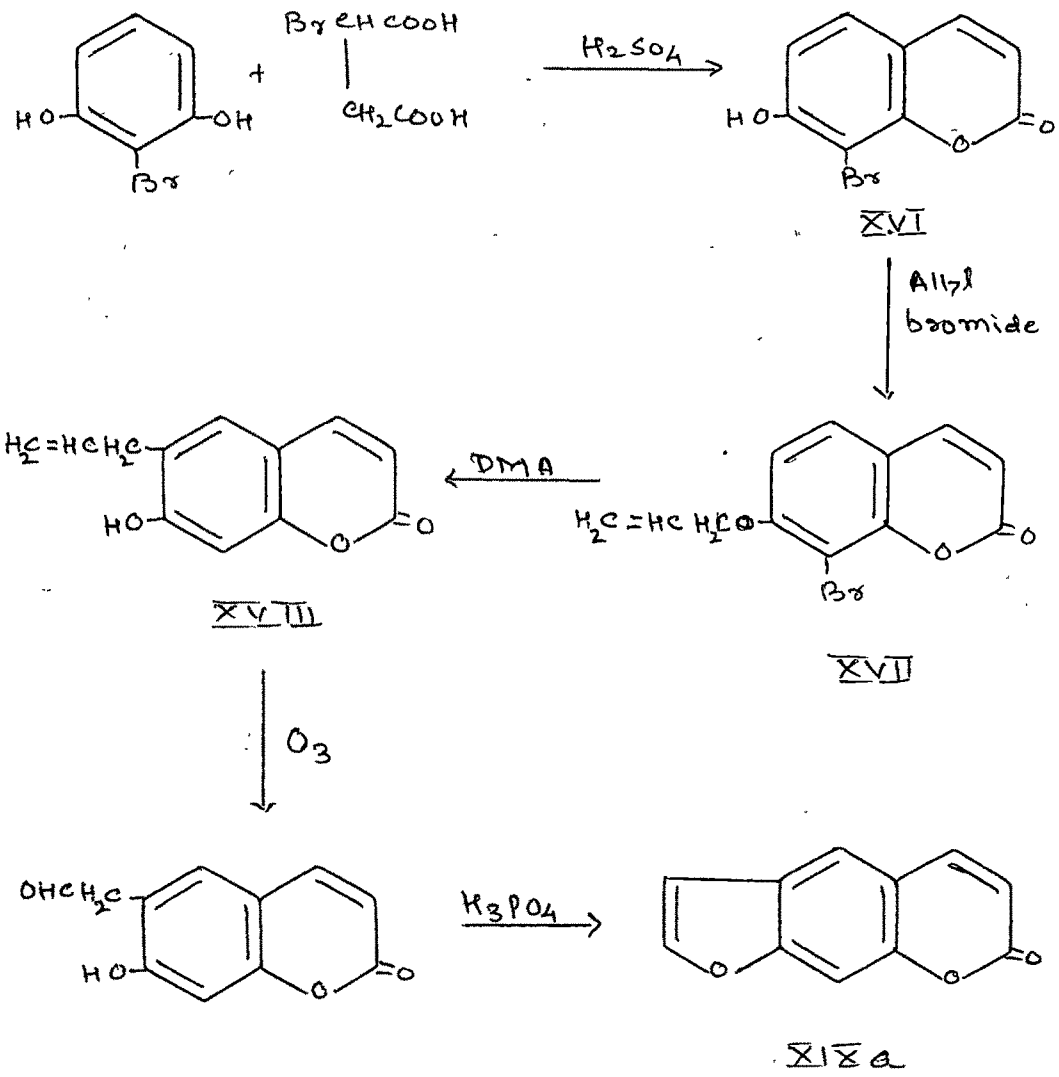


XIII XIV

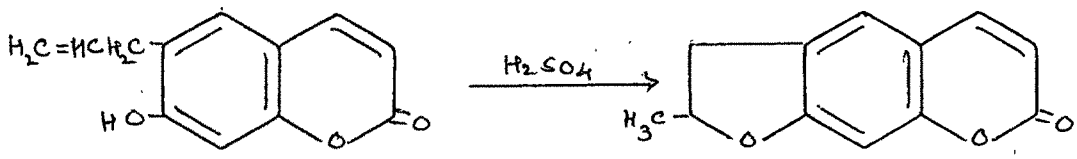
IV XV

demethylation gave 5-formyl-6-hydroxybenzofuran (XV) which was condensed with diethyl malonate to furnish psoralene(IV), after hydrolysis and decarboxylation of the Knoevenagel product.

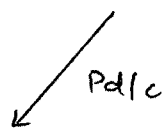
Pardanani and Trivedi[19] synthesised psoralene and alkyl psoralene. Pechmann condensation of 2-bromoresorcinol with malic acid gave 7-hydroxy-8-bromocoumarin (XVI), which was allylated to 7-allyloxy-8-bromocoumarin (XVII). This was

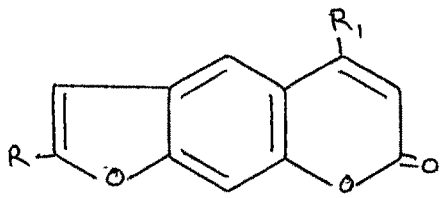


refluxed with dimethylaniline in an atmosphere of nitrogen to give 6-allyl-7-hydroxycoumarin (XVIII). Ozonolysis of (XVIII) gave an acetaldehydo derivative which on cyclisation with o-phosphoric acid gave psoralene (XIXa). (XVIII) on cyclisation with conc. sulphuric acid gave dihydro derivative (XX) which was subsequently dehydrogenated by refluxing with diphenyl ether in the presence of palladised charcoal (10 %) to give 2-methyl-7-oxo-7H-furano(3,2-g)benzopyran (XIXb).



XVIII XX





XIX

(a) $R=R_1=R_2=H$

(b) $R=CH_3$; $R_1=R_2=H$

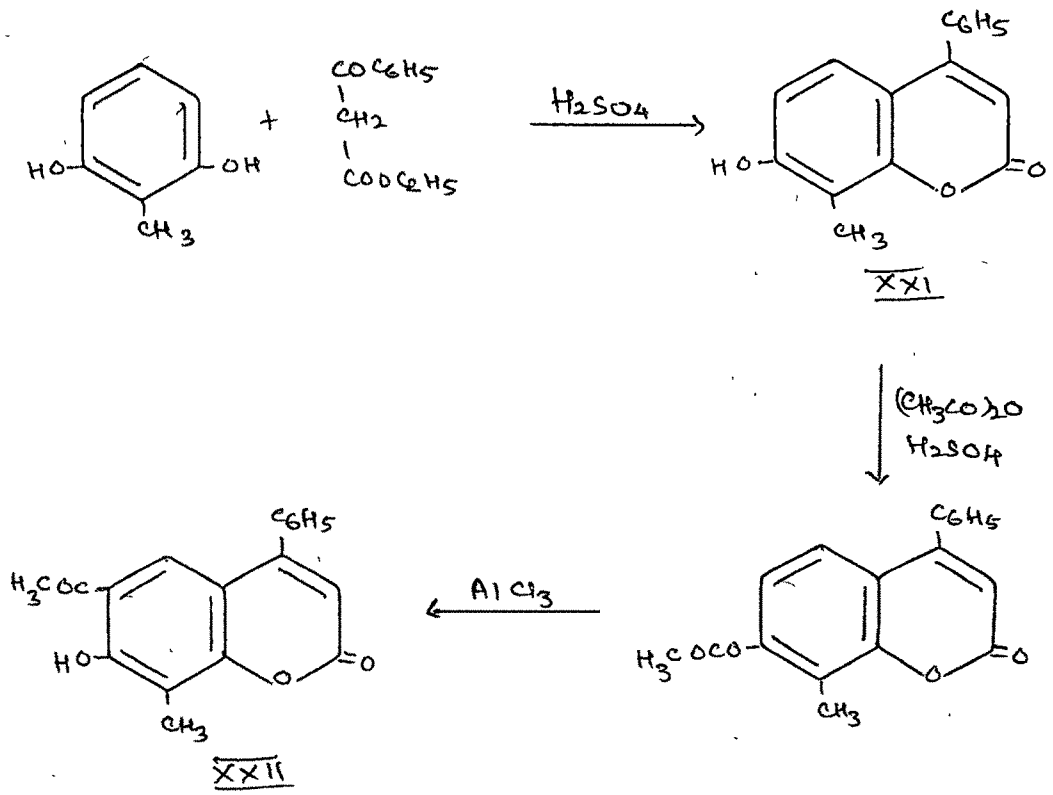
(c) $R=R_2=H$; $R_1=CH_3$

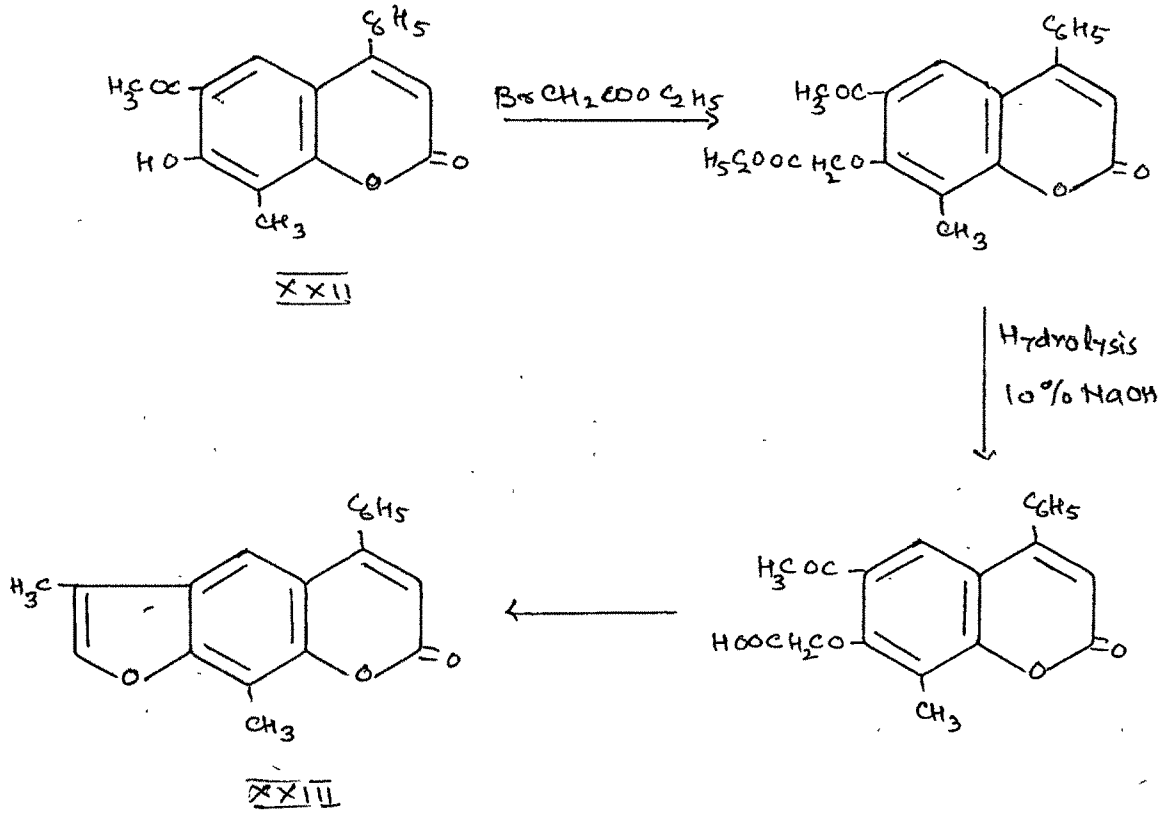
(d) $R=R_1=CH_3$; $R_2=H$

(e) $R=H$; $R_1=C_6H_5$; $R_2=CH_3$.

Pechmann condensation of 2-bromoresorcinol with ethyl acetoacetate and ethyl benzoylacetate gave 7-hydroxy-8-bromo-4-methylcoumarin and 7-hydroxy-8-bromo-4-phenylcoumarin respectively. These were subjected to the above series of reactions to give (XIXc, XIXd and XIXe).

Pardanani and Trivedi[20] have also carried out the Pechmann condensation of 2-methylresorcinol with ethyl benzoylacetate to give 7-hydroxy-8-methyl-4-phenylcoumarin (XXI). This on acylation and subsequent Fries migration gave 7-hydroxy-6-acyl-8-methyl-4-phenylcoumarin (XXII), which on condensation with ethyl bromoacetate followed by hydrolysis and cyclisation gave the corresponding psoralene derivative (XXIII).

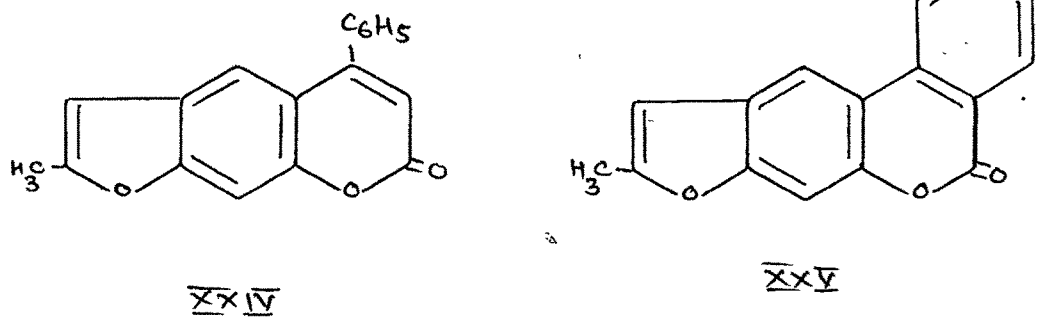




XXII

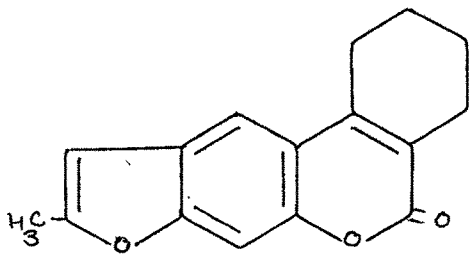
XXIII

Shah and Trivedi[21] have recently synthesised 2-methyl-5-phenyl-7H-furano(3,2-g)benzopyran-7-one (XXIV), 9-methyl-5H-benzofurano(6,5-c)benzopyran-5-one (XXV), 9-methyl--1,2,3,4-tetrahydro-5H-benzofurano(6,5-c)benzopyran-5-one(XXVI)

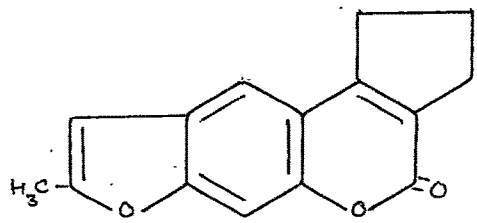


XXIV

XXV



XXVI

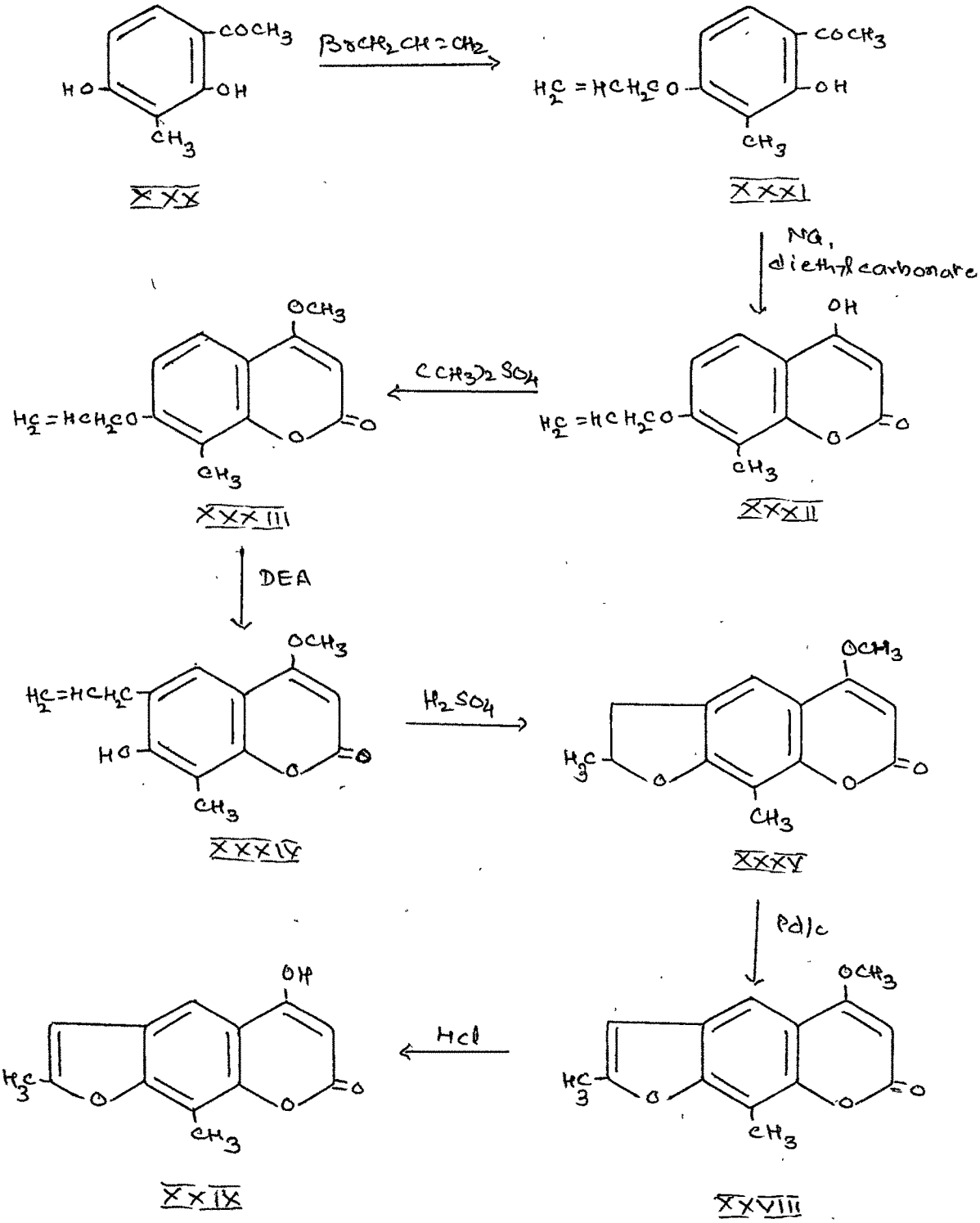


XXVII

and 8-methyl-1,2,3,4-tetrahydrocyclopenta(c)furano(2,3-g)-benzopyran-4-one (XXVII) by the same method as described above.

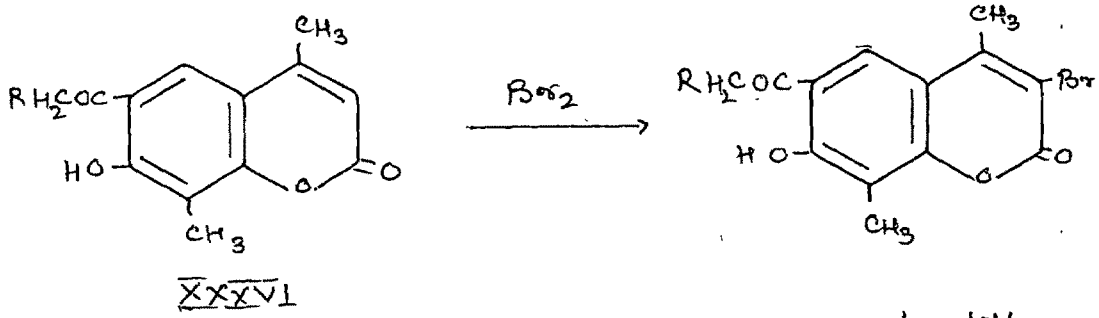
Dholakia and Trivedi[22] synthesised 4-methoxy-5',8-dimethylpsoralene (XXVIII) and 4-hydroxy-5',8-dimethylpsoralene (XXIX). 2,4-Dihydroxy-3-methylacetophenone (XXX) was allylated with allyl bromide to 4-allyloxy-2-hydroxy-3-methylacetophenone (XXXI) which on condensation with diethyl carbonate in the presence of pulverised sodium yielded 4-hydroxy-7-allyloxy-8-methylcoumarin (XXXII). This was methylated to its methylether derivative (XXXIII) which was subjected to Claisen rearrangement by refluxing it with diethylaniline to give 4-methoxy-6-allyl-7-hydroxy-8-methylcoumarin (XXXIV). The cyclisation of (XXXIV) gave 4-methoxy-5',8-dimethyl-4',5'-dihydropsoralene (XXXV) by triturating it with conc. sulphuric acid which was further dehydrogenated to 4-methoxy-5',8-dimethylpsoralene (XXVIII) by refluxing it with diphenylether in the presence of palladised charcoal (10 %).

It underwent demethylation when refluxed with conc. hydrochloric acid to give 4-hydroxy-5',8-dimethylpsoralene (XXIX).



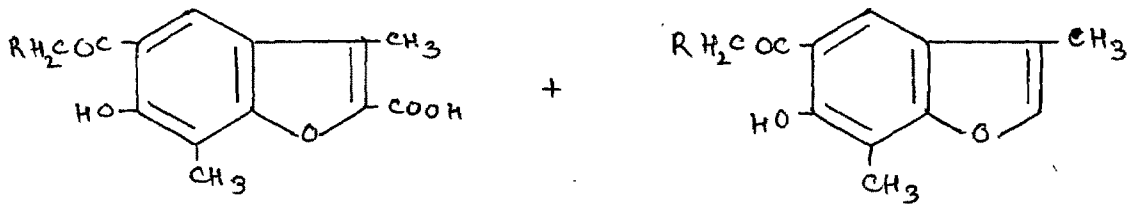
XXX XXXI XXXII XXXIII XXXIV XXXV XXXVI XXXVII XXXVIII XXXIX

Shaikh and Trivedi[23] prepared 4-hydroxy-4',8-dimethylpsoralene (XXXIXa) and 4-hydroxy-3,8,,4'-trimethylpsoralene (XXXIXb). 4,8-Dimethyl-7-hydroxy-6-acylcoumarin (XXXVI) on



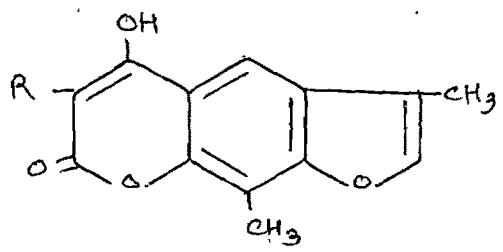
XXXVI

10% Na_2CO_3



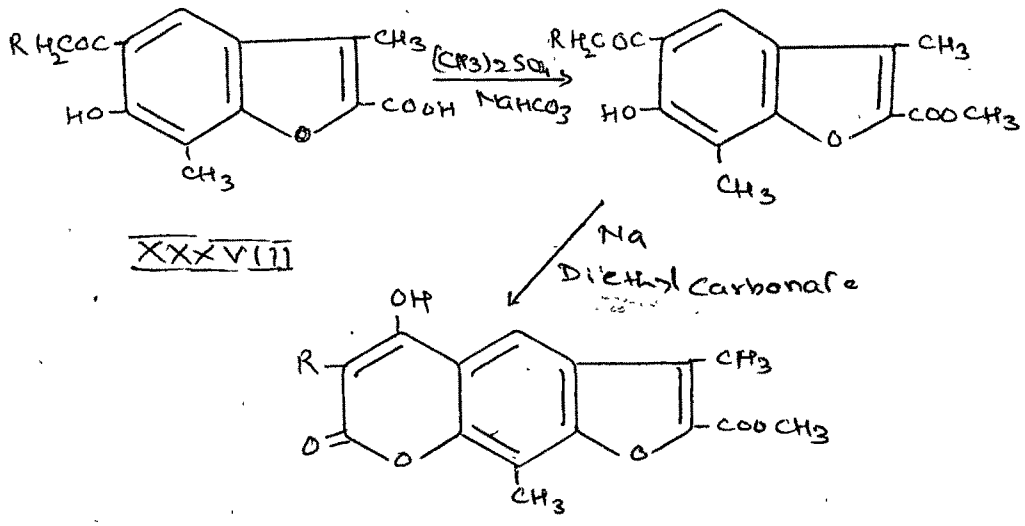
XXXVIII XXXVII

Na, Diethyl carbonate



XXXIX (a) R=H

(b) R=CH_3



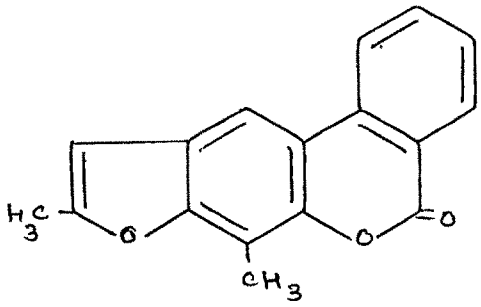
XL (a) R=H

(b) R=CH_3

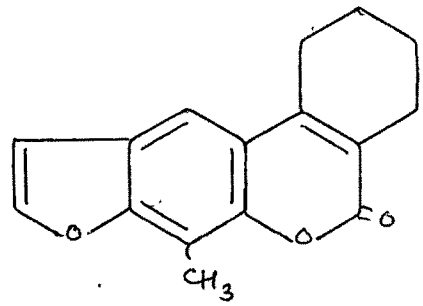
bromination followed by hydrolysis with sodium carbonate (10 %) yielded 3,7-dimethyl-6-hydroxy-5-acylcoumarone (XXXVII) and 3,7-dimethyl-6-hydroxy-5-acylcoumaron-2-carboxylic acid (XXXVIII). (XXXVII), on condensation with diethyl carbonate in the presence of pulversied sodium gave (XXXIXa) and (XXXIXb).

Esterification of (XXXVIII) with dimethyl sulphate in the presence of sodium bicarbonate and acetone followed by the condensation with diethyl carbonate in the presence of pulverised sodium gave (XLa) and (XLb).

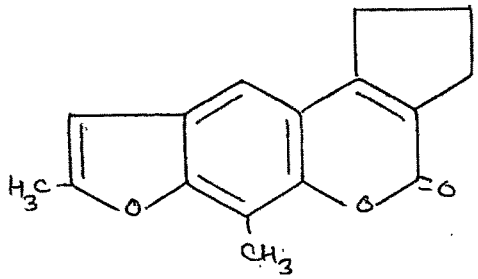
Shaikh and Trivedi[24] have also prepared 2,9-dimethyl--7-oxo-7H-furano(3,2-g)benzo(c)benzopyran (XLI), 9-methyl-5,6--cyclohexano-7-oxo-7H-furano(3,2-g)benzopyran (XLII), 2,9-dimethyl-5,6-cyclopentano-7-oxo-7H-furano(3,2-g)benzopyran (XLIII) and 9-methyl-5,6-cyclopentano-7-oxo-7H-furano(3,2-g)benzopyran (XLIV).



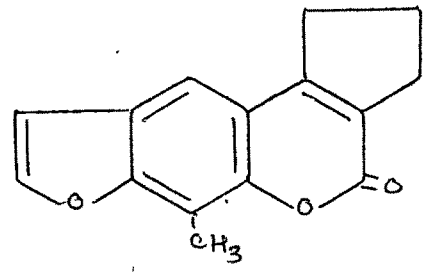
XLI



XLII



XLIII



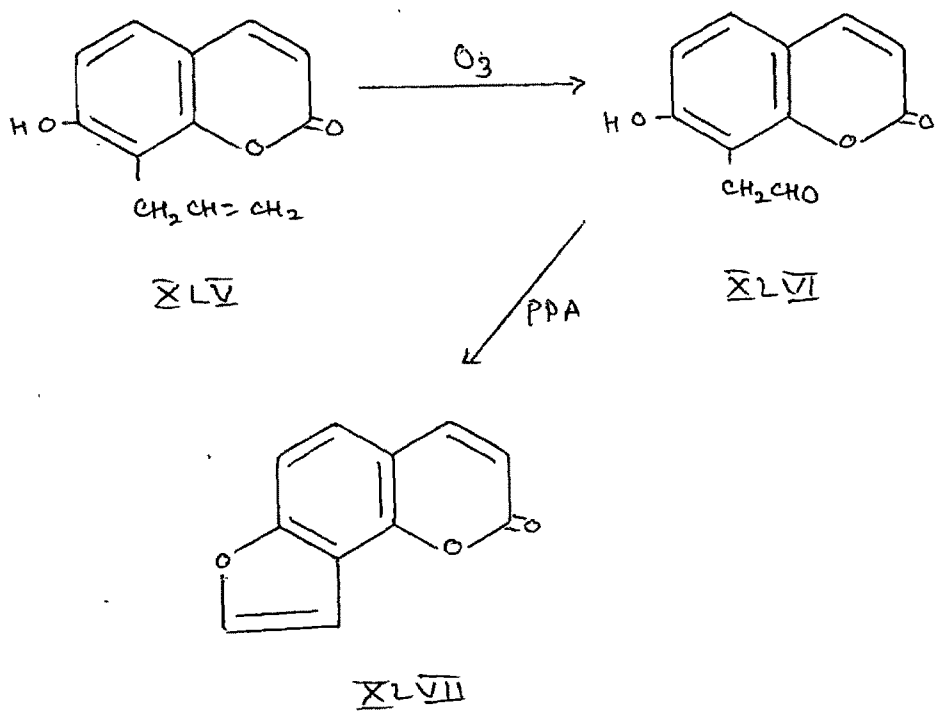
XLIV

Angelicin (XLVII), a naturally occurring furano-coumarin - an angular one of type (G), was first synthesised by Spath and Pailer[25] by condensing sodium salt of umbelli-feron-8-aldehyde with iodoacetic aester under pressure and the product thus obtained was subjected to hydrolysis followed by cyclisation.

Naik and Thakore[26] synthesised this using ethyl bromoacetate and acetone. Using the same method Shah and Shah[27] prepared 3-methyl-5-oxo-5H-furano(2,3-h)benzopyran (furano-3'-methyl-4',5',8,7-coumarin) from 7-hydroxy-8-acetylcoumarin.

Limaye[28] synthesised Angelicin by preparing 4-hydroxy-5-formylcoumarone from 4-hydroxycoumarone and subjecting it to Perkin reaction.

Aneja, Mukherjee and Seshadri[16] synthesised angelicin by subjecting first 7-hydroxy-8-allylcoumarin (XLV) to ozonolysis and subsequent cyclisation of 7-hydroxycoumarin--8-acetaldehyde (XLVI) with polyphosphoric acid.



XLV XLVI XLVII

In continuation of the work on the synthesis of furanocoumarins carried out in our laboratory, the following furanocoumarins, both angular as well as linear, are synthesised to study their photodynamic activity.

(1) 7-Hydroxy-2-methyl-6-phenyl-5-oxo-5H-furano(2,3-h)benzopyran (LV).

(2) 7-Hydroxy-2-methyl-6-(p-methoxyphenyl)-5-oxo-5H-furano-(2,3-h)benzopyran (LXIV).

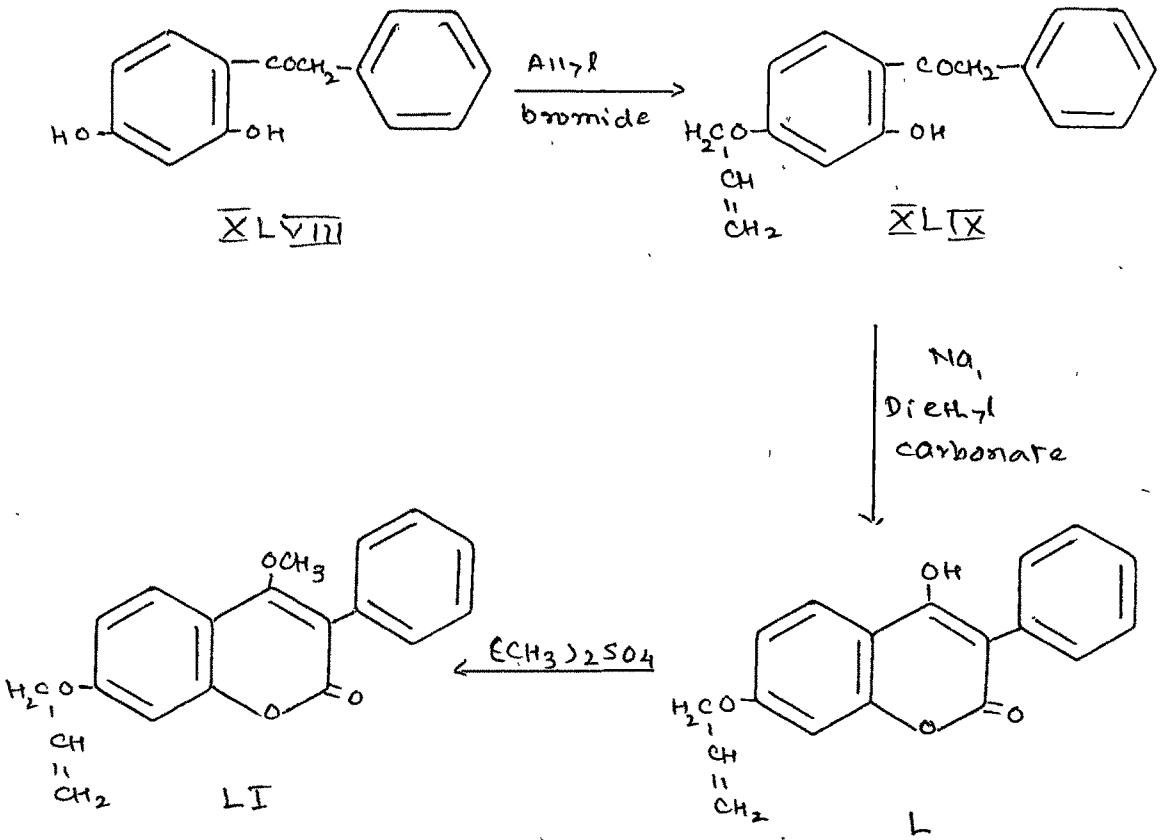
(3) 2,9-Dimethyl-5-hydroxy-6-phenyl-7-oxo-7H-furano(3,2-g)-benzopyran (LXX).

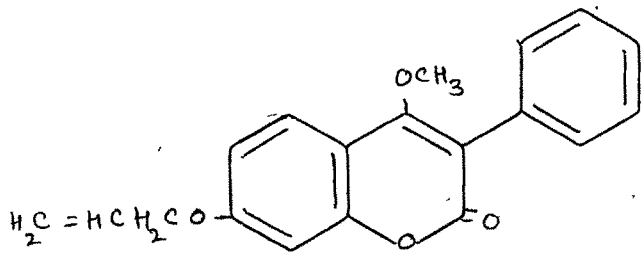
Synthesis of 7-hydroxy-2-methyl-6-phenyl-5-oxo-5H-furano(2,3-h)benzopyran

Using the procedure of Dholakia and Trivedi[22], synthesis of 7-hydroxy-2-methyl-6-phenyl-5-oxo-5H-furano-(2,3-h)benzopyran (LV) is achieved as under :-

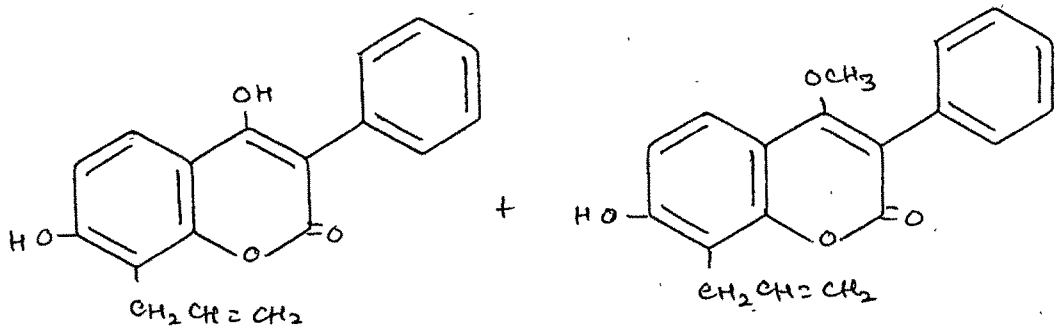
2,4-Dihydroxyphenylbenzyl ketone (XLVIII) was allylated with allyl bromide in the presence of anhydrous potassium carbonate in acetone. 4-Allyloxy-2-hydroxyphenylbenzyl ketone (XLIX) was then condensed with diethyl carbonate in the presence of pulverised sodium to give 7-allyloxy-3-phenyl-4-hydroxycoumarin (L). This was then methylated to 7-allyloxy-4-methoxy-3-phenylcoumarin (LI) which on Claisen rearrangement gave three products. The ethereal solution on washing with sodium bicarbonate solution yielded 8-allyl-4,7-dihydroxy-3-phenylcoumarin (LII) on acidification. The ethereal solution on washing with dilute sodium hydroxide solution gave 8-allyl-7-hydroxy-4-methoxy-3-phenylcoumarin (LIII) and the ethereal solution on evaporation gave an original allyloxy derivative (LI). The products (LII and LIII), on cyclisation with conc.

sulphuric acid gave the same product which was soluble in sodium bicarbonate solution, and it was assigned the structure 2,3-dihydro-7-hydroxy-2-methyl-6-phenyl-5-oxo-5H-furano(2,3-h)--benzopyran (LIV). This was refluxed with palladised charcoal (10 %) in diphenylether to give 7-hydroxy-2-methyl-6-phenyl--5-oxo-5H-furano(2,3-h)benzopyran (LV). Attempt to carry out oxidative dehydrogenation with palladised charcoal and air of (LIV) to furanocoumestan derivative according to the procedure of Thomas Kappe et al.[29] failed, only (LV) was obtained.

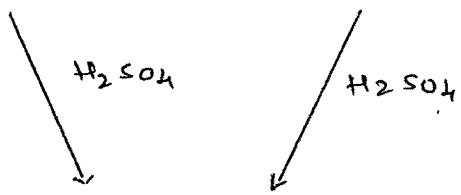


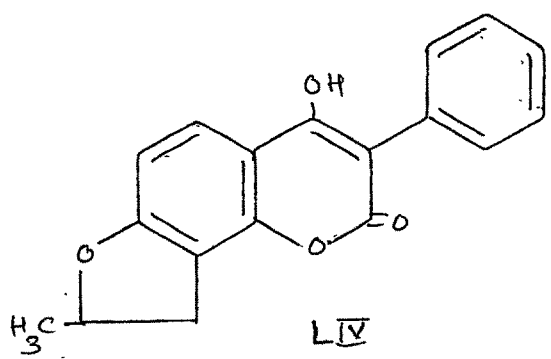


LI

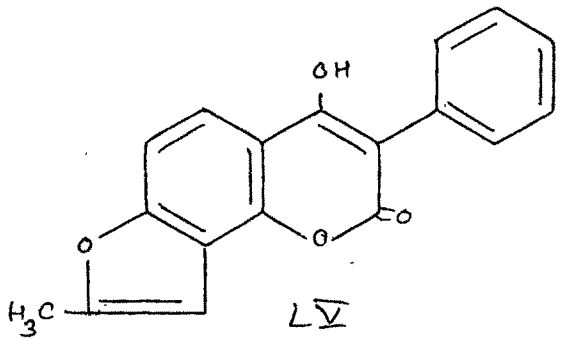


LII LIII

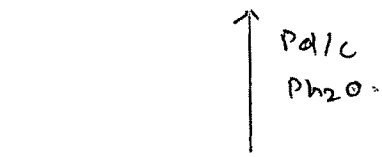


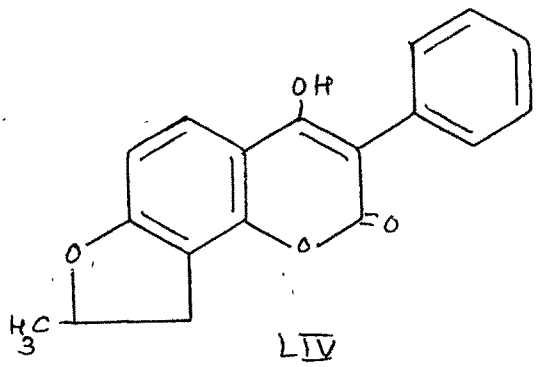


LIV

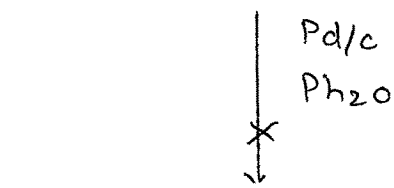


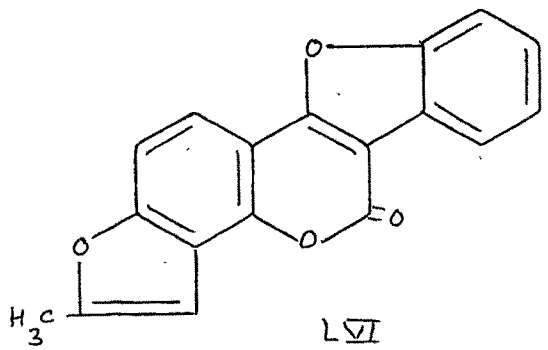
LV





LIV

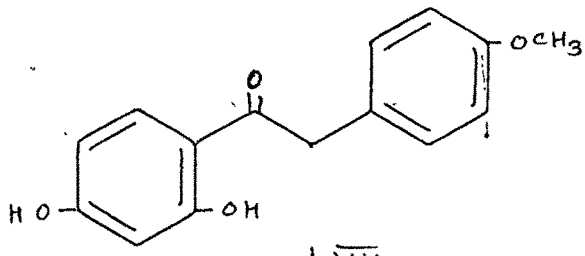




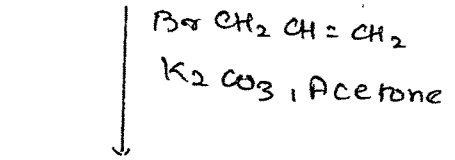
LVI

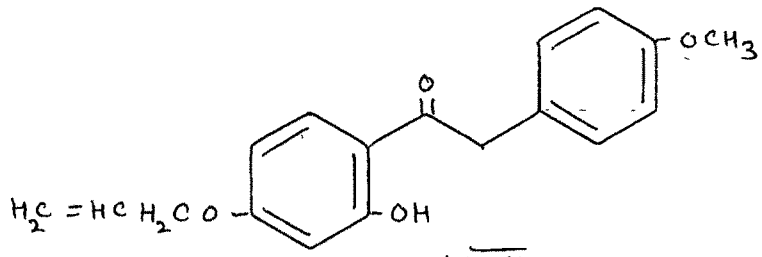
Synthesis of 7-hydroxy-2-methyl-6-(p-methoxyphenyl)--5-oxo-5H-furano(2,3-h)benzopyran

2,4-Dihydroxy(p-methoxyphenyl)benzyl ketone (LVII) was condensed with allyl bromide in the presence of potassium carbonate to give 4-allyloxy-2-hydroxy(p-methoxy-phenyl)benzyl ketone (LVIII) which was further reacted with ethyl carbonate in the presence of pulverised sodium to give 7-allyloxy-4-hydroxy-3-(p-methoxyphenyl)coumarin (LIX). This was then methylated to 7-allyloxy-4-methoxy-3-(p-methoxyphenyl)-coumarin (LX) with dimethyl sulphate. (LX) was subjected to Claisen rearrangement by refluxing it with dimethylaniline. Three products were obtained by separating chemically. The ethereal solution was washed successively with sodium bicarbonate solution and dilute sodium hydroxide solution. Sodium bicarbonate solution on acidification gave 8-allyl--4,7-dihydroxy-3-(p-methoxyphenylcoumarin (LXI) and sodium hydroxide solution on acidification gave 8-allyl-7-hydroxy-4--methoxy-3-(p-methoxyphenyl)coumarin (LXII). The ethereal solution on evaporation gave unchanged (LX). (LXI and LXII) were triturated with conc. sulphuric acid to give 2,3-dihydro--7-hydroxy-2-methyl-6-(p-methoxyphenyl)-5-oxo-5H-furano(2,3-h) benzopyran (LXIII). This did not undergo dehydrogenation with palladised charcoal (10 %) to give 7-hydroxy-2-methyl-6--(p-methoxyphenyl)-5-oxo-5H-furano(2,3-h)benzopyran (LXIV).

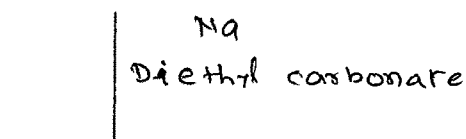


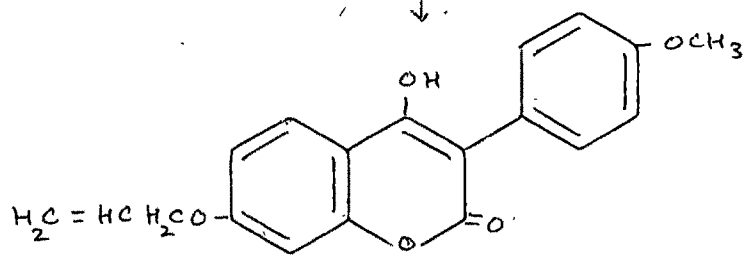
LVII



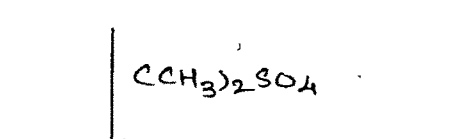


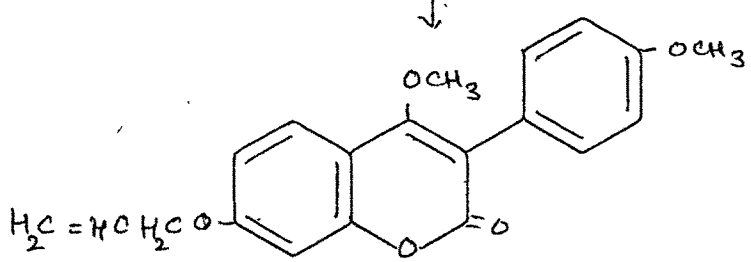
LVIII



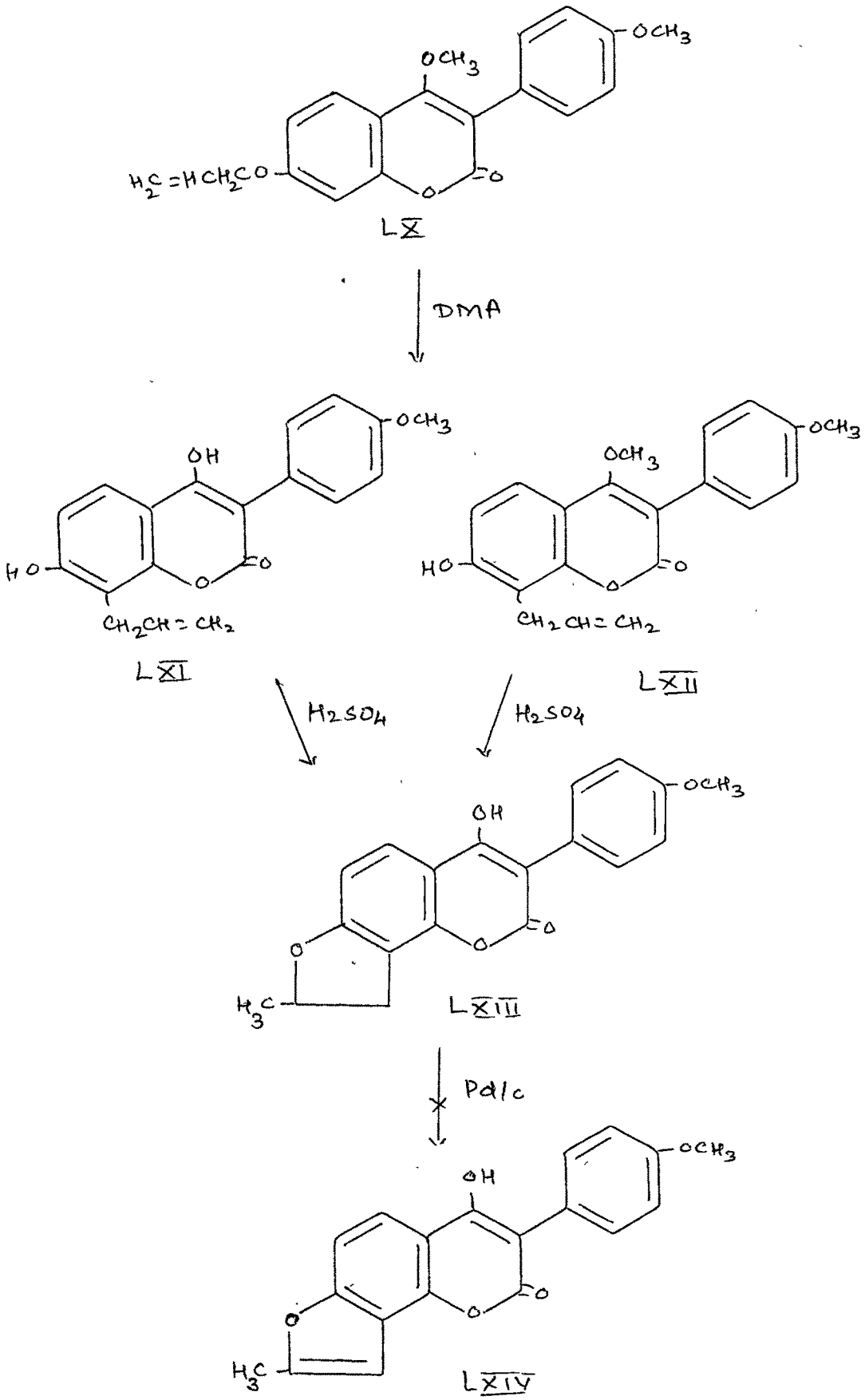


LIX



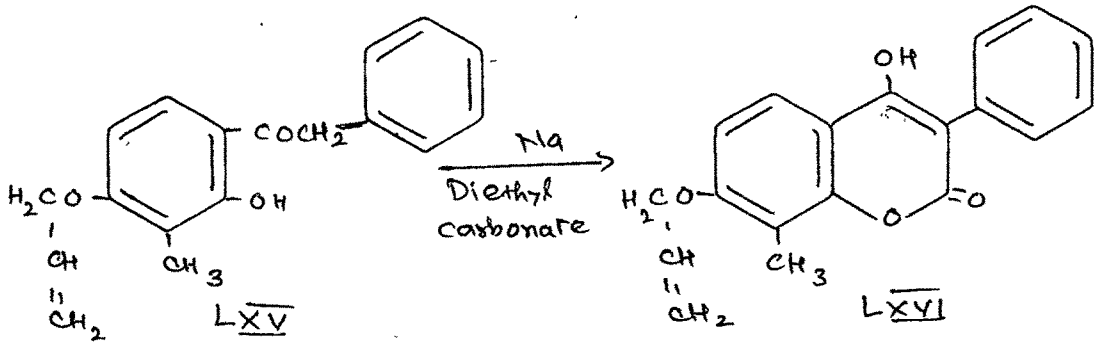


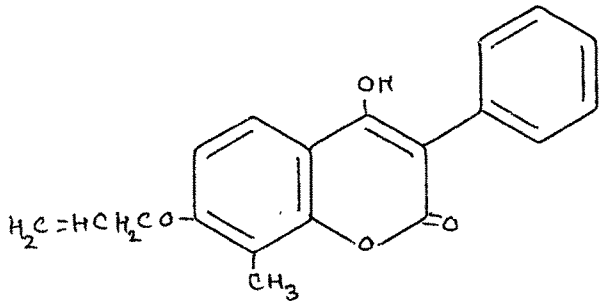
LX


OCH3
OCH3
H2C=HCH2CO
O
LX
DMA
OCH3
OH
HO
O
O
CH2CH=CH2
LXI
OCH3
OCH3
HO
O
O
CH2CH=CH2
LXII
H2SO4
H2SO4
OCH3
OH
O
O
O
H3C
LXIII
Pd/c
OCH3
OH
O
O
O
H3C
LXIV

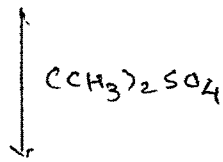
Synthesis of 2,9-dimethyl-5-hydroxy-6-phenyl-7-oxo-7H--furano(3,2-g)benzopyran

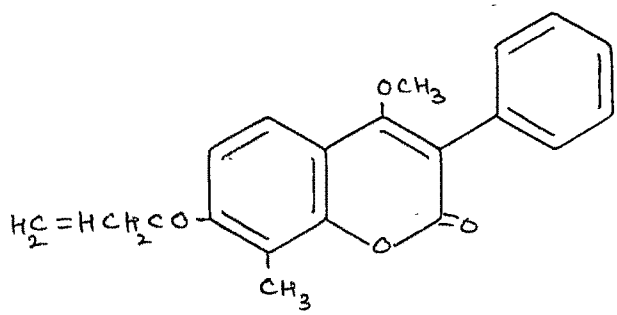
Condensation of 4-allyloxy-2-hydroxy-3-methylphenylbenzyl ketone[22] (LXV) with diethyl carbonate in the presence of pulverised sodium gave 7-allyloxy-8-methyl-3--phenyl-4-hydroxycoumarin (LXVI). This was methylated to its 4-methoxy derivative (LXVII). The Claisen rearrangement of 7-allyloxy-4-methoxy-8-methyl-3-phenylcoumarin gave three products. The separation was affected by treating the ethereal solution of the mixture, first with sodium bicarbonate solution, which on acidification yielded 6-allyl-4,7-dihydroxy-8-methyl--3-phenylcoumarin (LXVIII) and second with sodium hydroxide solution on acidification gave 6-allyl-7-hydroxy-8-methyl-3-phenyl-4-methoxycoumarin (LXIX). The ethereal solution on evaporation gave an unconverted (LXVII). (LXVIII and LXIX) were then cyclised with conc. sulphuric acid to give 2,9-dimethyl-5-hydroxy-6-phenyl-2,3-dihydro-7-oxo-7H-furano(3,2-g)-benzopyran (LXX). This was then dehydrogenated in the presence of palladised charcoal (10 %) by refluxing it with diphenyl-ether to give 2,9-dimethyl-5-hydroxy-6-phenyl-7-oxo-7H-furano--(3,2-g)benzopyran (LXXI).



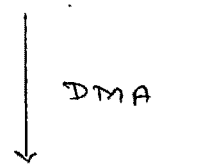


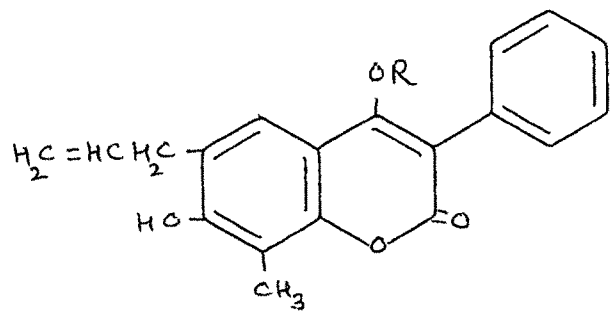
LXVI





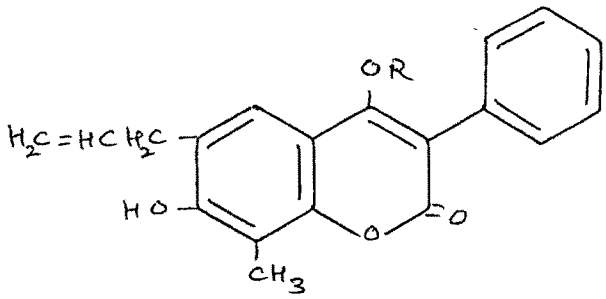
LXVII





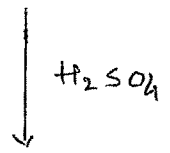
LXVIII R = H

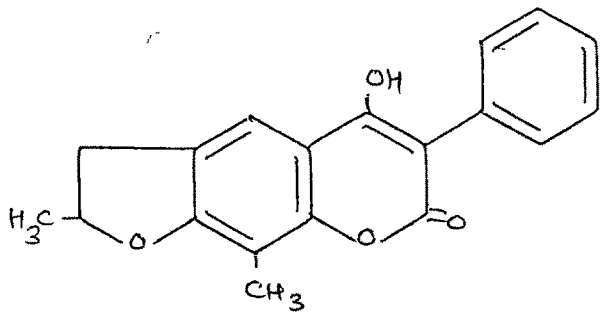
LXIX R = CH_3



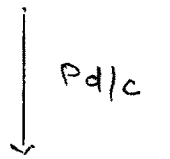
LXVIII R = H

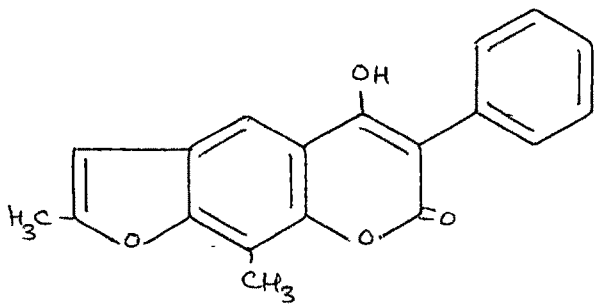
LXIX R = CH_3





LXX





LXXI

EXPERIMENTAL

7-Hydroxy-2-methyl-6-phenyl-5-oxo-5H-furano(2,3-h)benzopyran (LV) : 7-Allyloxy-3-phenyl-4-hydroxycoumarin (L) :

4-Allyloxy-2-hydroxyphenylbenzyl ketone was prepared by the allylation of 2,4-dihydroxyphenylbenzyl ketone according to the method of Dholakia and Trivedi[22].

A solution of 4-allyloxy-2-hydroxyphenylbenzyl ketone (2.0 g.) in diethyl carbonate (15 ml.) was added slowly to the pulverised sodium (2.0 g.) and the mixture was heated on a water bath for 12 hr. Alcohol was added to the mixture to decompose the unreacted sodium and the solution was added to the crushed ice. The solution was filtered and the filtrate on acidification gave a solid, 7-allyloxy-3-phenyl-4-hydroxy-coumarin, crystallised from chloroform, m.p. 195°. Yield 2.0 g.

Analysis : Found : C, 73.05 ; H, 4.93 %

$C_{18}H_{14}O_4$ requires : C, 73.47 ; H, 4.78 %.

Methylation of 7-allyloxy-3-phenyl-4-hydroxycoumarin : 7-Allyloxy-4-methoxy-3-phenylcoumarin (LI) :

7-Allyloxy-3-phenyl-4-hydroxycoumarin (2.0 g.) was refluxed with dimethyl sulphate (2 ml.) and anhydrous potassium carbonate (6.0 g.) in dry acetone (50 ml.) on a water bath for 3 hr. Acetone was removed by distillation and the residue was diluted with water. The solid separated was filtered and crystallised from benzene-petroleum ether mixture,

m.p. 85-86°. Yield 2.0 g.

Analysis : Found : C, 73.52 ; H, 5.61 %

$C_{19}H_{16}O_4$ requires : C, 73.05 ; H, 5.19 %.

Claisen rearrangement of 7-allyloxy-4-methoxy-3-phenylcoumarin : 8-Allyl-4,7-dihydroxy-3-phenylcoumarin (LII) : 8-allyl-7--hydroxy-4-methoxy-3-phenylcoumarin (LIII) :

7-Allyloxy-4-methoxy-3-phenylcoumarin (2.0 g.) was refluxed with dimethylaniline (15 ml.) for 6 hr. The reaction mixture was added to the ice-cold dilute hydrochloric acid solution. The whole solution was then extracted with ether. The ethereal layer was first extracted with sodium bicarbonate solution (3x100 ml.) which on acidification with hydrochloric acid gave a solid, 8-allyl-4,7-dihydroxy--3-phenylcoumarin, crystallised from methanol, m.p. 193°. Yield 0.06 g.

Analysis : Found : C, 73.69 ; H, 4.93 %

$C_{18}H_{14}O_4$ requires : C, 73.47 ; H, 4.78 %.

The ethereal solution was washed with sodium hydroxide solution which on acidification with hydrochloric acid gave 8-allyl-7-hydroxy-4-methoxy-3-phenylcoumarin, crystallised from alcohol, m.p. 191-2°. Yield 0.8 g.

IR (nujol) : 3400 $cm.^{-1}$ (hydroxyl group), 1680 $cm.^{-1}$ (carbonyl stretching frequency), 1610 $cm.^{-1}$ (aromatic -C=C- stretching frequency) and 910 $cm.^{-1}$ ($>C=CH_2$ stretching frequency).

Analysis : Found : C, 74.22 ; H, 4.92 %

$C_{19}H_{16}O_4$ requires : C, 74.02 ; H, 5.19 %.

The ethereal solution on evaporation yielded unchanged 7-allyloxy-4-methoxy-3-phenylcoumarin. The compound was characterised by its mixed m.p. with the original compound.

Cyclisation of 8-allyl-4,7-dihydroxy-3-phenylcoumarin and 8-allyl-7-hydroxy-4-methoxy-3-phenylcoumarin : 7-Hydroxy-2-methyl-6-phenyl-2,3-dihydro-5-oxo-5H-furano(2,3-h)benzopyran (LIV) :

8-Allyl-4,7-dihydroxy-3-phenylcoumarin (0.5 g.) was triturated with sulphuric acid (80 % ; 5 ml.) on a water bath for 10 minutes and the solution was poured into the crushed ice. The solid separated was filtered and purified by dissolving in sodium bicarbonate solution. The filtrate on acidification gave a solid, 7-hydroxy-2-methyl-6-phenyl-2,3-dihydro-5-oxo-5H-furano(2,3-h)benzopyran, crystallised from aqueous alcohol, m.p. 224-25°. Yield 0.2 g.

IR (nujol) : 3300 $cm.^{-1}$ (hydroxyl group), 1660 $cm.^{-1}$ (carbonyl stretching frequency) and 1620 $cm.^{-1}$ (aromatic -C=C- stretching frequency).

Analysis : Found : C, 71.80 ; H, 4.73 %

$C_{18}H_{14}O_4.1/2\ H_2O$ requires : C, 71.22 ; H, 4.95 %.

8-Allyl-7-hydroxy-4-methoxy-3-phenylcoumarin also gave the same product (LIV), on treating it with sulphuric acid (80 %). The m.p. and mixed m.p. with the above compound remained the same, i.e. 225°.

7-Hydroxy-2-methyl-6-phenyl-5-oxo-5H-furano(2,3-h)benzo--pyran (LV) :

7-Hydroxy-2-methyl-6-phenyl-2,3-dihydro-5-oxo--5H-furano(2,3-h)benzopyran (0.5 g.) was refluxed with diphenylether (10 ml.) and palladised charcoal (10 % ; 0.3 g.) for 10 hr. on a wire gauze. The solution was cooled and petroleum ether was added after the removal of the catalyst. The solid separated, 7-hydroxy-2-methyl-6-phenyl-5-oxo-5H-furano(2,3-h)benzopyran, was crystallised from ethyl acetate-petroleum ether mixture, m.p. 208°. Yield 0.2 g.

Analysis : Found : C, 73.50 ; H, 4.62 %

$C_{18}H_{12}O_4$ requires : C, 73.97 ; H, 4.19 %.

7-Hydroxy-2-methyl-6-(p-methoxyphenyl)-5-oxo-5H-furano(2,3-h)--benzopyran (LXIV) : 7-Allyloxy-3-(p-methoxyphenyl)-4-hydroxycoumarin (LIX) :

A solution of 4-allyloxy-2-hydroxy(p-methoxyphenyl)benzyl ketone (2.5 g.) in diethyl carbonate (15 ml.) was added to the pulverised sodium (2.5 g.) and the mixture was heated on a water bath for 12 hr. The mass was diluted with alcohol and the solution was poured into the ice-cold water. The solution was filtered and the filtrate on acidification with hydrochloric acid gave a solid, 7-allyloxy--3-(p-methoxyphenyl)-4-hydroxycoumarin, crystallised from alcohol, m.p. 166-68°. Yield 2.0 g.

Analysis : Found : C, 71.03 ; H, 4.89 %

$C_{19}H_{16}O_5$ requires : C, 70.40 ; H, 4.92 %.

Methylation of 7-allyloxy-3-(p-methoxyphenyl)-4-hydroxy--coumarin : 7-Allyloxy-4-methoxy-3-(p-methoxyphenyl)--coumarin (LX) :

7-Allyloxy-3-(p-methoxyphenyl)-4-hydroxycoumarin (2.0 g.) was refluxed with dimethyl sulphate (3 ml.) and anhydrous potassium carbonate (6.0 g.) in dry acetone (50 ml.) for 3 hr. on a water bath. The solid obtained after evaporation of the solvent and subsequent dilution with water, was crystallised from benzene-petroleum ether mixture, m.p. 110°. Yield 2.0 g.

Analysis : Found : C, 71.46 ; H, 5.62 %

$C_{20}H_{18}O_5$ requires : C, 71.00 ; H, 5.32 %.

Claisen rearrangement of 7-allyloxy-4-methoxy-3-(p-methoxy--phenyl)coumarin : 8-Allyl-4,7-dihydroxy-3-(p-methoxyphenyl)--coumarin (LXI) and 8-allyl-7-hydroxy-4-methoxy-3-(p-methoxy--phenyl)coumarin (LXII) :

7-Allyloxy-4-methoxy-3-(p-methoxyphenyl)coumarin (2.0 g.) was refluxed with dimethylaniline (15 ml.) for 6 hr.. The mixture was then added to the dilute hydrochloric acid solution and extracted with ether. The ethereal solution was then extracted with sodium bicarbonate solution which on acidification gave 8-allyl-4,7-dihydroxy-3-(p-methoxyphenyl)--coumarin, crystallised from aqueous alcohol, which decomposes at 184° and melts at 210°. Yield 0.4 g.

IR (nujol) : 3400 $cm.^{-1}$ (hydroxyl group), 1655 $cm.^{-1}$ (carbonyl stretching frequency) and 940 $cm.^{-1}$ ($>C=CH_2$ stretching frequency).

Analysis : Found : C, 71.03 ; H, 5.26 %

$C_{19}H_{16}O_5$ requires : C, 70.40 ; H, 4.92 %.

The ethereal solution on extraction with sodium hydroxide solution followed by its acidification gave 8-allyl--7-hydroxy-4-methoxy-3-(p-methoxyphenyl)coumarin, crystallised from alcohol, m.p. 207-8°. Yield 0.8 g.

IR (mujol) : 3400 $cm.^{-1}$ (hydroxyl group) and 1665 $cm.^{-1}$ (carbonyl stretching frequency).

Analysis : Found : C, 71.47 ; H, 5.34 %

$C_{20}H_{18}O_5$ requires : C, 71.00 ; H, 5.32 %.

The ethereal solution on evaporation gave unchanged 7-allyloxy-4-methoxy-3-(p-methoxyphenyl)coumarin. The compound was characterised by its mixed m.p. with the original compound.

Cyclisation of 8-allyl-4,7-dihydroxy-3-(p-methoxyphenyl)-coumarin and 8-allyl-7-hydroxy-4-methoxy-3-(p-methoxy--phenyl)coumarin : 7-Hydroxy-2-methyl-6-(p-methoxyphenyl)--2,3-dihydro-5-oxo-5H-furano(2,3-h)benzopyran (LXIII) :

8-Allyl-4,7-dihydroxy-3-(p-methoxyphenyl)coumarin (0.5 g.) was triturated with sulphuric acid (5 ml.; 80 %) on a water bath for 10 minutes. The solution was then added to the crushed ice and the solid separated was filtered, crystallised from ethyl acetate-petroleum ether mixture, m.p. 212°. Yield 0.2 g.

Similarly, 8-allyl-7-hydroxy-4-methoxy-3-(p-methoxy-phenyl)coumarin (0.5 g.) was cyclised by triturating with sulphuric acid (5 ml.; 80 %) and worked out as above. It gave

7-hydroxy-2-methyl-6-(p-methoxyphenyl)-2,3-dihydro-5-oxo--5H-furano(2,3-h)benzopyran, m.p. 210-11°. The mixed m.p. did not depress with the product obtained as above.

Analysis : Found : C, 68.77 ; H, 5.02 %

$C_{19}H_{16}O_5.1/2\ H_2O$ requires : C, 68.46 ; H, 5.10 %.

Attempted dehydrogenation of 7-hydroxy-2-methyl-6-(p-methoxy--phenyl)-5-oxo-5H-2,3-dihydrofurano(2,3-h)benzopyran : 7-Hydroxy-2-methyl-6-(p-methoxyphenyl)5-oxo-5H-furano(2,3-h)--benzopyran (LXIV) :

A mixture of 7-hydroxy-2-methyl-6-(p-methoxyphenyl)-2,3-dihydro-5-oxo-5H-furano(2,3-h)benzopyran (0.5 g.) and palladised charcoal (10 % ; 0.3 g.) in diphenylether (15 ml.) was refluxed on a wire gauze for longer period. The reaction mixture was filtered hot to remove the catalyst. The mother liquor on dilution with petroleum ether gave the original dihydro derivative which was characterised by its mixed m.p. and TLC.

2,9-Dimethyl-5-hydroxy-6-phenyl-7-oxo-7H-furano(3,2-g)benzo--pyran (LXXI) : 7-Allyloxy-8-methyl-3-phenyl-4-hydroxy--coumarin (LXVI) :

A solution of 4-allyloxy-3-methyl-2-hydroxyphenyl-benzyl ketone (2.0 g.) in diethyl carbonate (15 ml.) was carefully added to the pulverised sodium (2.5 g.) and the whole mixture was heated on the water bath for 12 hr. Alcohol was added to the reaction mixture to decompose the unreacted

sodium and the solution was added to the ice-cold water. The solution was filtered and the filtrate on acidification gave a solid, 7-allyloxy-8-methyl-3-phenyl-4-hydroxycoumarin, crystallised from benzene-petroleum ether mixture , m.p. 212-14°. Yield 2.0 g.

Analysis : Found : C, 74.49 ; H, 5.66 %

$C_{19}H_{16}O_4$ requires : C, 74.02 ; H, 5.19 %.

Methylation of 7-allyloxy-8-methyl-3-phenyl-4-hydroxycoumarin : 7-Allyloxy-4-methoxy-8-methyl-3-phenylcoumarin (LXVII) :

7-Allyloxy-8-methyl-3-phenyl-4-hydroxycoumarin (2.0 g.) was refluxed with dimethyl sulphate (2 ml.) and anhydrous potassium carbonate (6.0 g.) in dry acetone (80 ml.) on a water bath for 40 hr. The acetone was distilled off and the residue was treated with water. The solid separated was filtered and washed with water. The solid, 7-allyloxy-4-methoxy--8-methyl-3-phenylcoumarin, crystallised benzene-petroleum ether mixture, m.p. 130-31°. Yield 1.8 g.

Analysis : Found : C, 74.92 ; H, 6.02 %

$C_{20}H_{18}O_4$ requires : C, 74.53 ; H, 5.59 %.

Claisen rearrangement of 7-allyloxy-4-methoxy-8-methyl-3--phenylcoumarin : 6-Allyl-4,7-dihydroxy-8-methyl-3-phenylcoumarin (LXVIII) and 6-allyl-7-hydroxy-4-methoxy-8-methyl--3-phenylcoumarin (LXIX) :

7-Allyloxy-4-methoxy-8-methyl-3-phenylcoumarin (2.5 g.) was refluxed with dimethylaniline (15 ml.) for 6 hr.

The reaction mixture was poured into the ice-cold hydrochloric acid solution. The compound was extracted with ether and the ethereal solution was first washed with sodium bicarbonate solution which on acidification with hydrochloric acid gave 6-allyl-4,7-dihydroxy-8-methyl-3-phenylcoumarin, crystallised from benzene-petroleum ether mixture, m.p. 174-76°. Yield 0.4 g.

Analysis : Found : C, 74.22 ; H, 5.64 %

$C_{19}H_{16}O_4$ requires : C, 74.02 ; H, 5.19 %.

The ethereal solution was then washed with sodium hydroxide solution which on acidification gave 6-allyl-7-hydroxy-4-methoxy-8-methyl-3-phenylcoumarin, crystallised from benzene-petroleum ether mixture, m.p. 215-16°. Yield 0.6 g.

Analysis : Found : C, 74.42 ; H, 5.80 %

$C_{20}H_{18}O_4$ requires : C, 74.53 ; H, 5.59 %.

The ether layer on evaporation gave unchanged compound characterised by its mixed m.p. with the original compound.

Cyclisation of 6-allyl-4,7-dihydroxy-8-methyl-3-phenylcoumarin and 6-allyl-7-hydroxy-4-methoxy-8-methyl-3-phenylcoumarin : 2,9-Dimethyl-5-hydroxy-6-phenyl-2,3-dihydro-7-oxo-7H-furano-(3,2-g)benzopyran (LXX) :

6-Allyl-4,7-dihydroxy-8-methyl-3-phenylcoumarin (0.5 g.) on triturating with sulphuric acid (10 ml. ; 84 %)

on a water bath for 10 minutes gave 2,9-dimethyl-5-hydroxy--6-phenyl-2,3-dihydro-7-oxo-7H-furano(3,2-g)benzopyran, crystallised from benzene, m.p. 214-15°. Yield 0.3 g.

Similarly, 6-allyl-7-hydroxy-4-methoxy-8-methyl--3-phenylcoumarin (0.5 g.) was triturated with sulphuric acid (10 ml. ; 84 %) on a water bath for 10 minutes. The mixture was then poured into the crushed ice and the product separated was crystallised from benzene, m.p. 213-14°. Yield 0.25 g.

Analysis : Found : C, 73.52 ; H, 5.67 %

$C_{19}H_{16}O_4$ requires : C, 73.02 ; H, 5.29 %.

2,9-Dimethyl-5-hydroxy-6-phenyl-7-oxo-7H-furano(3,2-g)--benzopyran (LXXI) :

2,9-Dimethyl-5-hydroxy-6-phenyl-2,3-dihydro-7--oxo-7H-furano(3,2-g)benzopyran (0.5 g.) was refluxed with diphenylether (10 ml.) and palladised charcoal (10 % ; 0.3 g.) for 10 hr. on a wire gauze. The catalyst was removed by filteration and the filtrate on dilution with petroleum ether gave a solid, 2,9-dimethyl-5-hydroxy-6-phenyl-7-oxo-7H-furano(3,2-g)benzopyran, crystallised from alcohol, m.p. 258°. Yield 0.2 g.

Analysis : Found : C, 74.70 ; H, 4.66 %

$C_{19}H_{14}O_4$ requires : C, 74.50 ; H, 4.57 %.

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CHAPTER II

SECTION III

SYNTHESIS OF PYRANOFURANOCOUMARINS AND DIFURANOCOUMARIN

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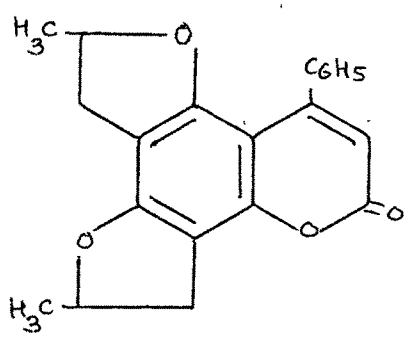
SYNTHESIS OF PYRANOFURANOCOUMARINS AND DIFURANOCOUMARIN

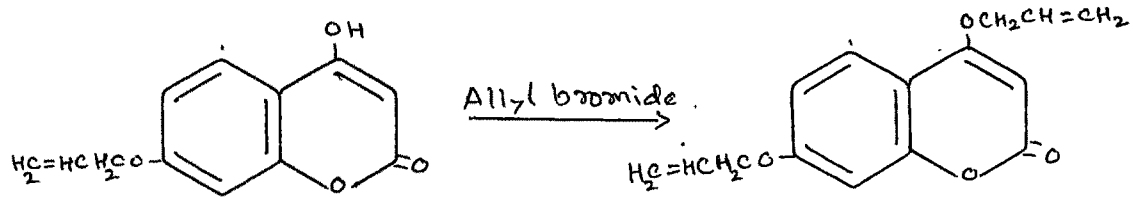
THEORETICAL

Furanocoumarins are of interest due to their valuable therapeutic properties and applicability in drugs. Furanocoumarins having furan ring fused with coumarin ring is reviewed in Chapter I, a part of it in Section II of the Chapter II and Chapter III.

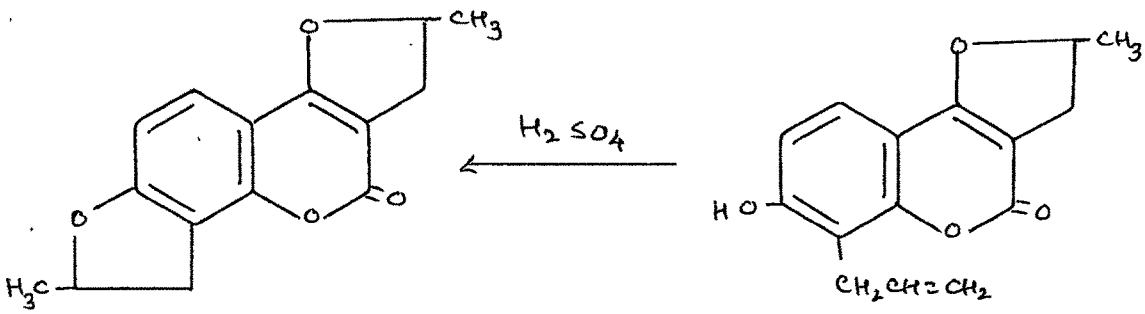
Seshadri et al.[1] have synthesised few difurano-coumarin derivatives. They have studied the Claisen migration of 5,7-dihydroxy-4-phenylcoumarin and obtained bis-2'-methyl-dihydrodifurano [4',5' : 5,6 and 4',5' : 7,8]-4-phenylcoumarin, the structure of which is represented as follows :-



Sanghvi and Trivedi[2] have also synthesised few difuranocoumarin derivatives. 4-Hydroxy-7-allyloxycoumarin (I) on allylation with allyl bromide gave 4,7-diallyloxy-coumarin (II). This was subjected to Claisen rearrangement by refluxing it with dimethylaniline to give (III) which on cyclisation with conc. sulphuric acid followed by dehydrogenation with palladised charcoal (10 %) in diphenyl-ether afforded 2,7-dimethyl-4-oxo-4H-difurano(3,2-c ; 2',3'-h)-benzopyran (IV).



I II



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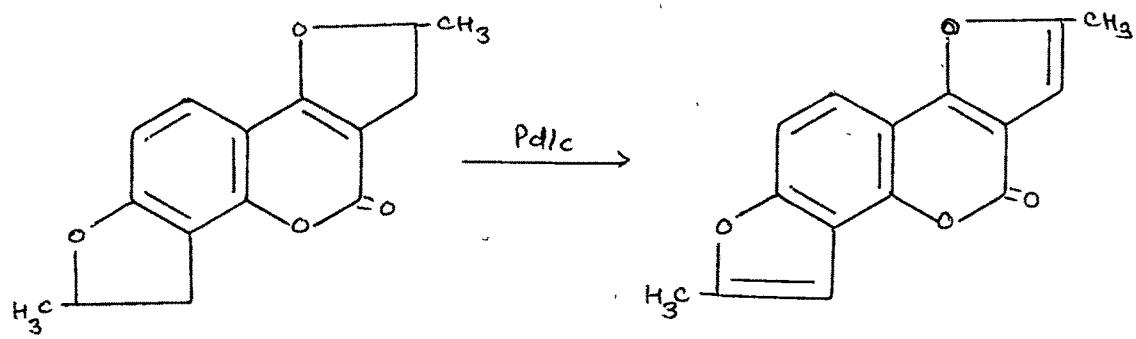
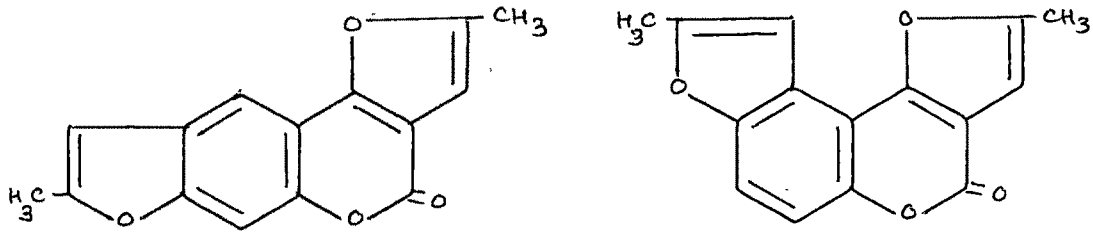


IV

Similarly, they have synthesised 2,6,8-trimethyl--4-oxo-4H-difurano(3,2-c ; 3',2'-g)benzopyran (V) and 2,9-dimethyl-4-oxo-4H-difurano(3,2-c ; 3',2'-f)benzopyran (VI).



V VI

In the present work the synthesis of few pyranofuranocoumarins and a difuranocoumarin is reported. The following pyranofuranocoumarins and difuranocoumarin derivatives are synthesised :-

(1) 2,8,8-Trimethyl-4-oxo-4H-furano(3,2-c)pyrano(2',3'-h)-benzopyran,

(2) 2,8,8-Trimethyl-4-oxo-4H-furano(3,2-c)pyrano(3',2'-g)-benzopyran,

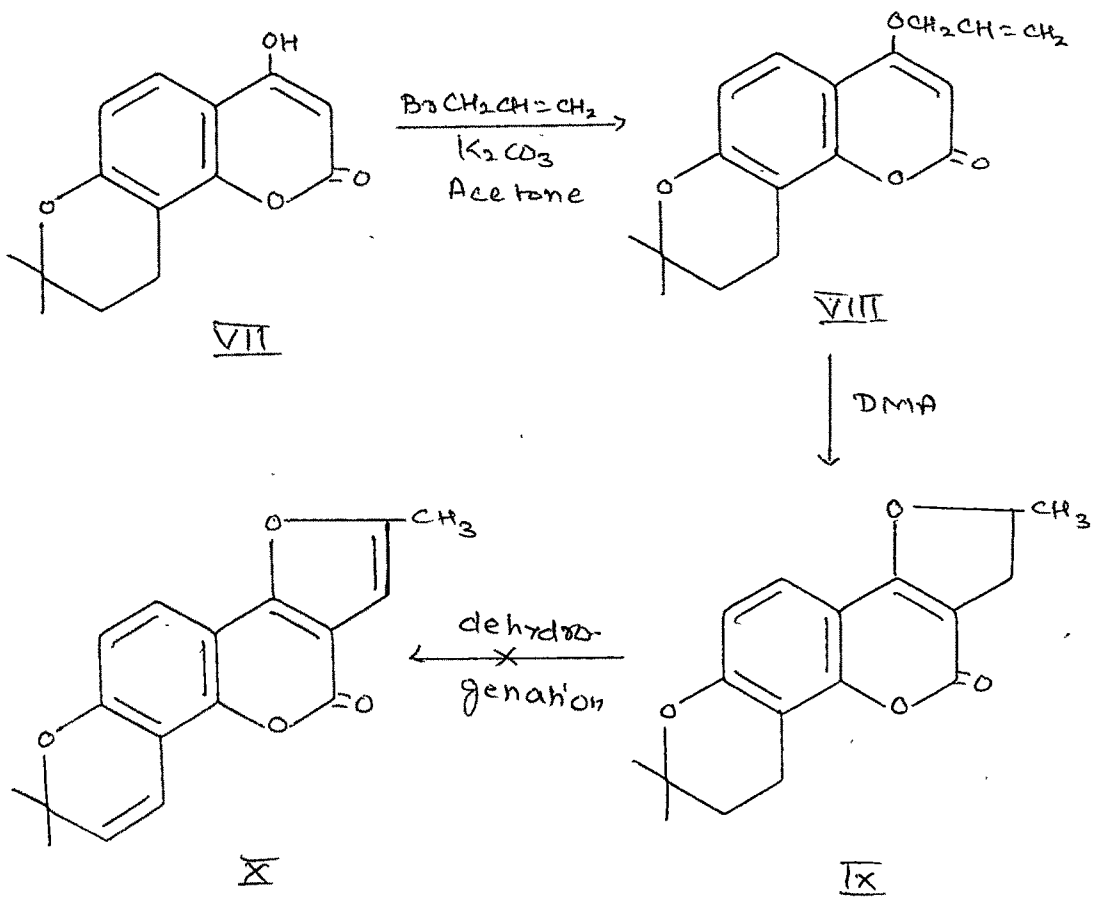
(3) 2,6,8,8,-Tetramethyl-4-oxo-4H-furano(3,2-c)pyrano--(3',2'-g)benzopyran and

(4) 2,3-Dihydro-4-oxo-4H-2,2,3,6,8-pentamethyldifurano--(3,2-c ; 3',2'-g)benzopyran.

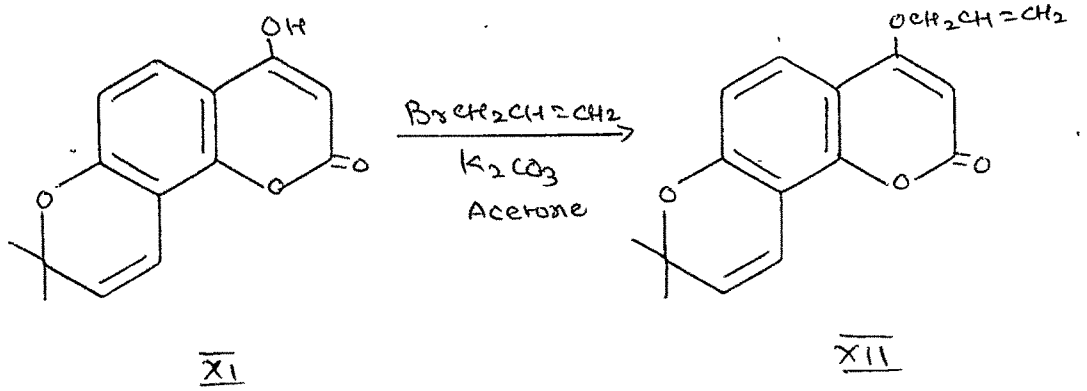
Synthesis of 2,8,8-trimethyl-4-oxo-4H-furano(3,2-c)--pyrano(2',3'-h)benzopyran

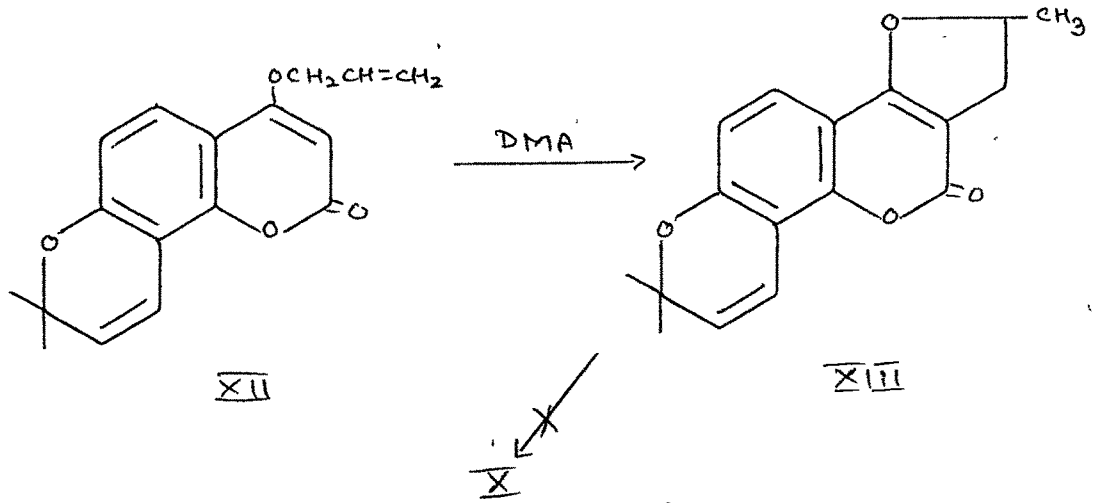
3,4-Dihydro-2,2-dimethyl-8-hydroxy-6-oxo-6H--pyrano(2,3-h)benzopyran,(VII) (prepared as described in Section I) was allylated with allyl bromide in the presence of anhydrous potassium carbonate and acetone to give 8-allyloxy-3,4-dihydro-2,2-dimethyl-6-oxo-6H-pyrano(2,3-h)-benzopyran (VIII). This on Claisen rearrangement by refluxing it with dimethylaniline yielded 2,3,6,7-tetrahydro--2,8,8-trimethyl-4-oxo-4H-furano(3,2-c)pyrano(2',3'-h)benzo-pyran (IX). This could not be dehydrogenated either with DDQ or palladised charcoal (10 %) to 2,8,8-trimethyl-4-oxo--4H-furano(3,2-c)pyrano(2',3'-h)benzopyran (X).

To prepare (X), 2,2-dimethyl-8-hydroxy-6-oxo-6H--pyrano(2',3'-h)benzopyran was allylated with allyl bromide to 8-allyloxy-2,2-dimethyl-6-oxo-6H-pyrano(2',3'-h)benzo-pyran (XII). This on Claisen migration by refluxing it with dimethylaniline gave 2,3-dihydro-2,8,8-trimethyl-4-oxo-4H--furano(3,2-c)pyrano(2',3'-h)benzopyran (XIII) which could



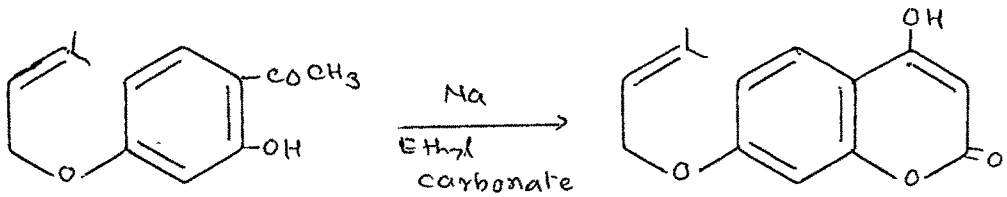
not be further dehydrogenated to (X). with DDQ or Pd/c.



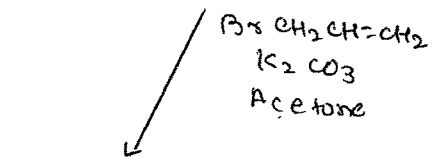


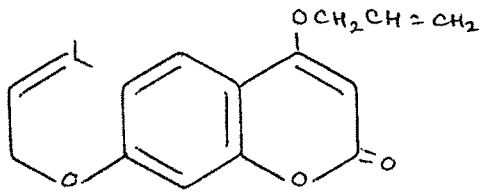
XII XIII X

2-Hydroxy-4-prenyloxyacetophenone (XIV) was condensed with diethyl carbonate in the presence of pulverised sodium to give 4-hydroxy-7-prenyloxycoumarin (XV). This was allylated with allyl bromide to 4-allyloxy-7-prenyloxycoumarin (XVI) which on Claisen rearrangement by refluxing with dimethylaniline gave 2,3-dihydro-2-methyl-7-prenyloxy-4-oxo--4H-furano(3,2-c)benzopyran (XVII). The structure of (XVII) was confirmed by its NMR spectrum in $CDCl_3$ which showed the signals at δ 1.78, doublet, J=7Hz, methyl group at position-2 ; 2.00, singlet, geminal dimethyl group; 3.25, multiplet, methylene group at position-3 of furan ring; 4.80, doublet, J=8Hz, two protons of CH_2=CH group; 5.40, multiplet, one proton at position-2; 5.65, multiplet, one proton of CH_2=CH group and 7.00-7.70, multiplet, three protons aromatic. (Fig.1) This (XVII) on further migration with dimethylaniline gave 2,3,6,7-tetrahydro-2,8,8-trimethyl-4--oxo-4H-furano(3,2-c)pyrano(2',3'-h)benzopyran (IX). This could not be dehydrogenated to (X).

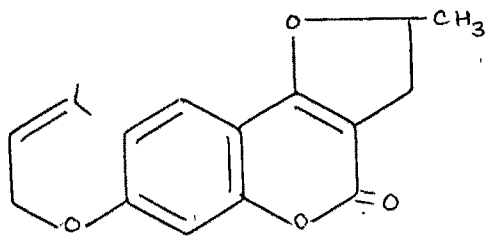


XIV XV

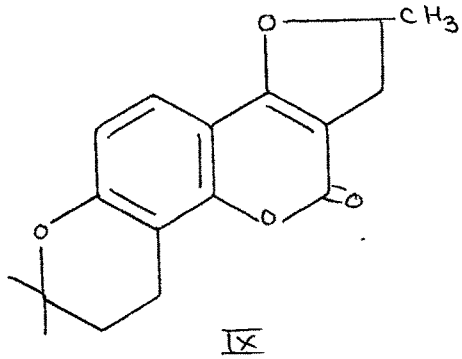




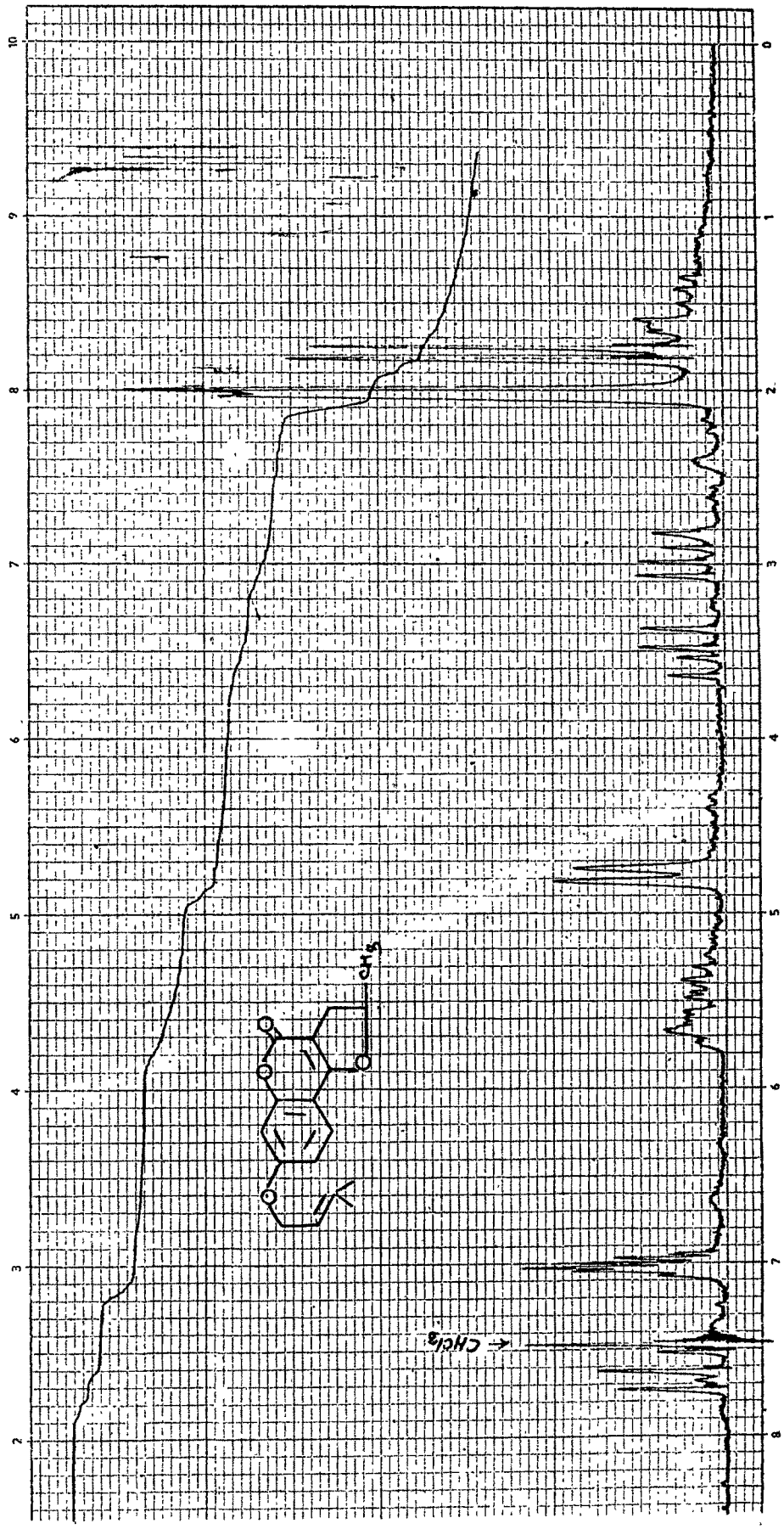
XVI



XVII



IX

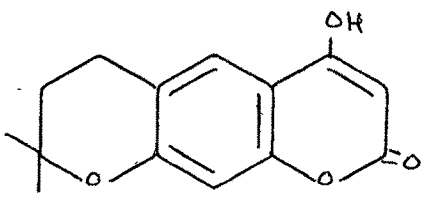


(Fig. 1) : 2,3-Dihydro-2-methyl-7-prenyloxy-4-oxo-4H-furano(3,2-c)benzopyran

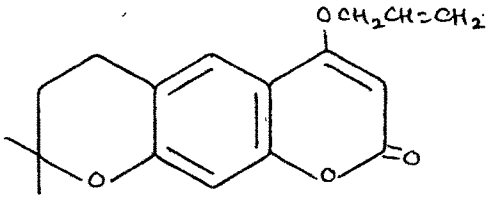
Synthesis of 2,8,8-trimethyl-4-oxo-4H-furano(3,2-c)-pyrano(3',2'-g)benzopyran

3,4-Dihydro-2,2-dimethyl-6-hydroxy-8-oxo-8H-pyrano(3,2-g)benzopyran (XVIII) (Section I), was allylated with allyl bromide in the presence of anhydrous potassium carbonate in acetone to give 3,4-dihydro-2,2-dimethyl-6-allyloxy-8-oxo-8H-pyrano(3,2-g)benzopyran (XIX). This on Claisen rearrangement in dimethylaniline gave 2,3,9,10-tetrahydro-2,8,8-trimethyl-4-oxo-4H-furano(3,2-c)pyrano(3',2'-g)-benzopyran (XX). This could not give the dehydrogenated product (XXI). The NMR spectrum of (XX) in $CDCl_3$ showed the following signals :-

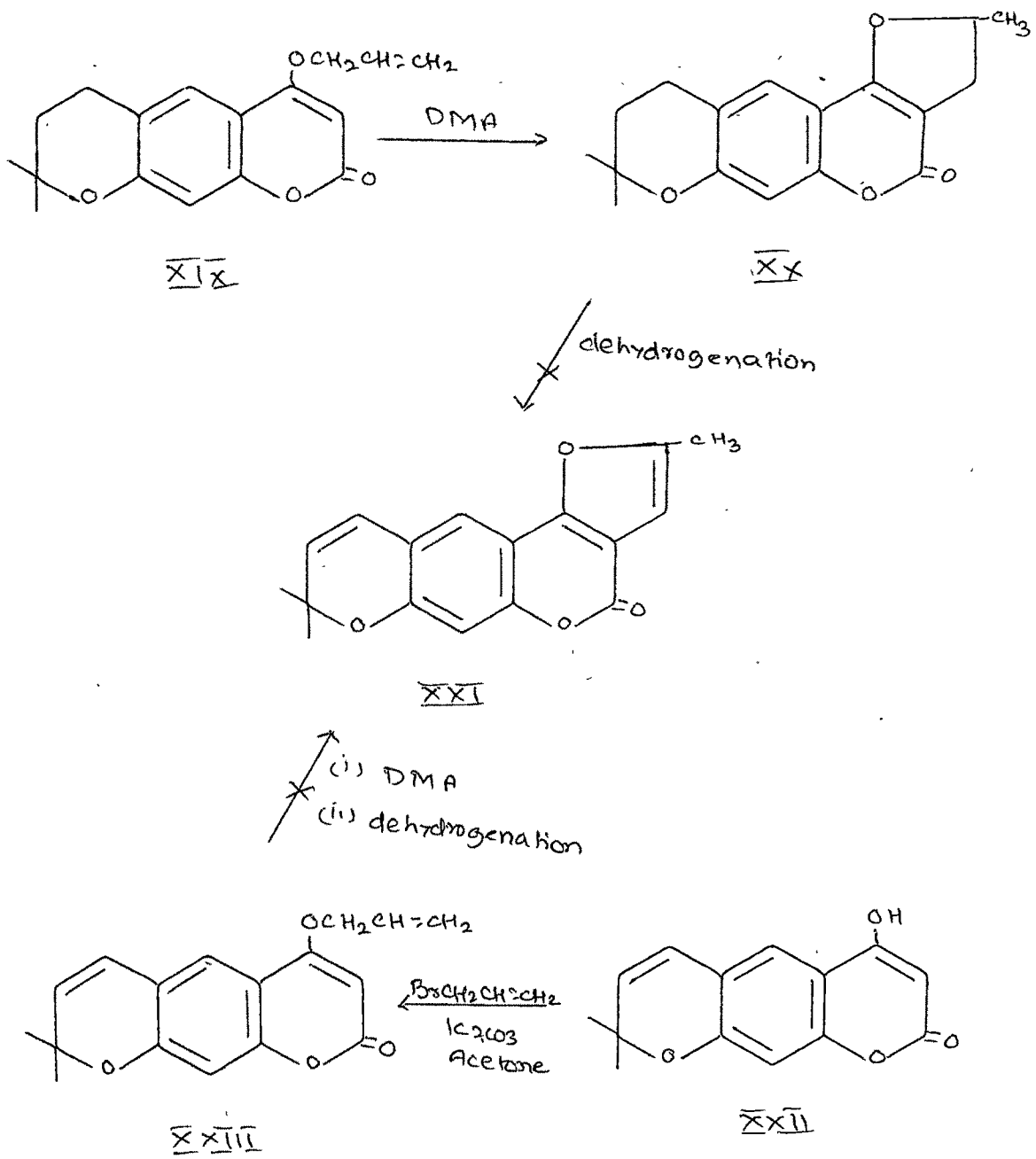
δ 1.50, singlet, geminal dimethyl group at position-8; 1.68, doublet, J=7Hz, methyl group at position-2; 1.98 and 2.98, two triplets, two methylene groups at position-9 and -10; 3.35, doublet, methylene group at position-3; 5.35, multiplet, one proton at position-2 and 6.85 and 7.40, two singlets, two protons aromatic at positions-6 and -11. (Fig. 2)



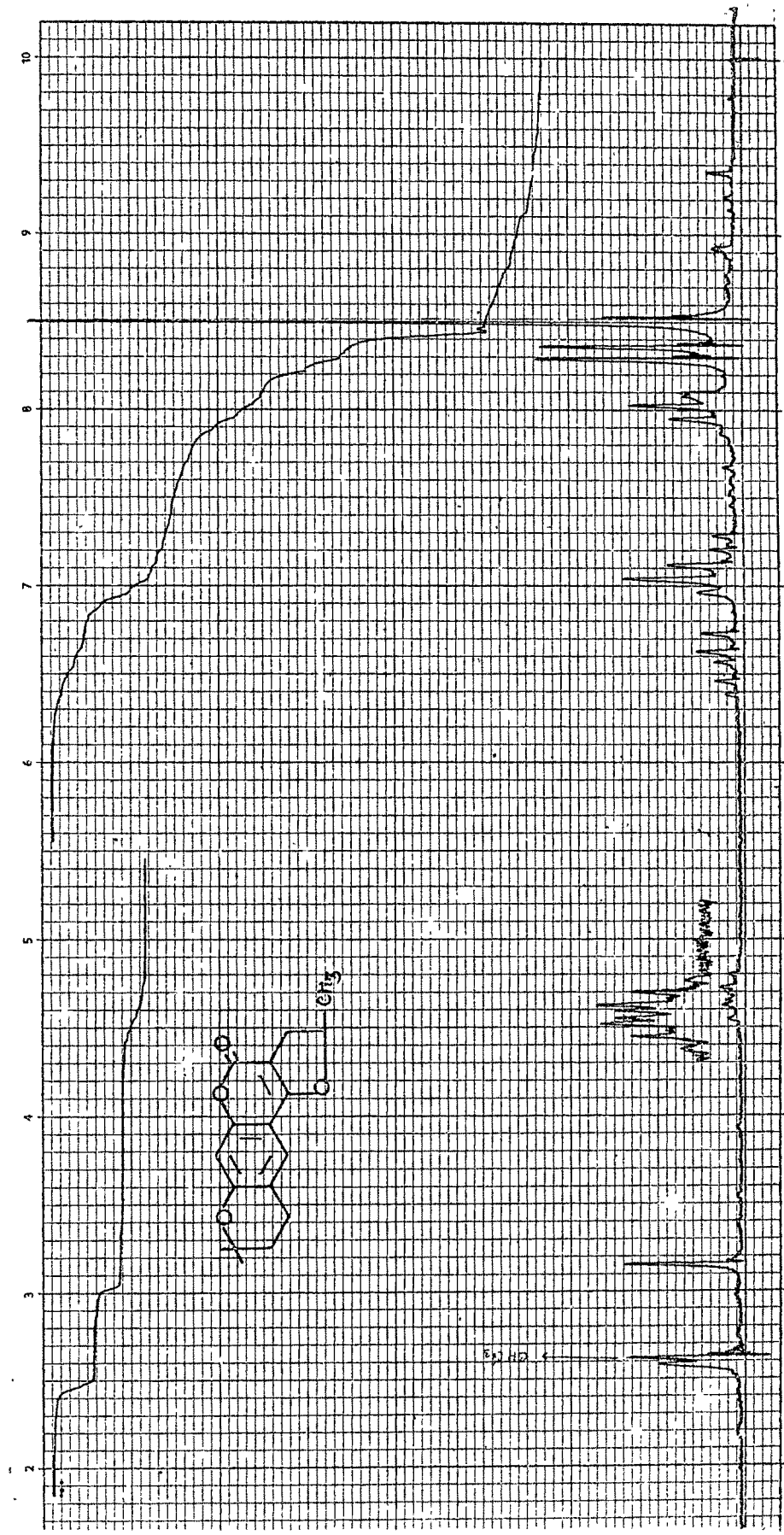
XVIII



XIX



To synthesise the dehydrogenated product (XXI), 2,2-dimethyl-6-hydroxy-8-oxo-8H-pyrano(3,2-g)benzopyran (XXII) was first allylated with allyl bromide which gave an oily product (XXIII) which on Claisen migration gave an unidentifiable oily product.



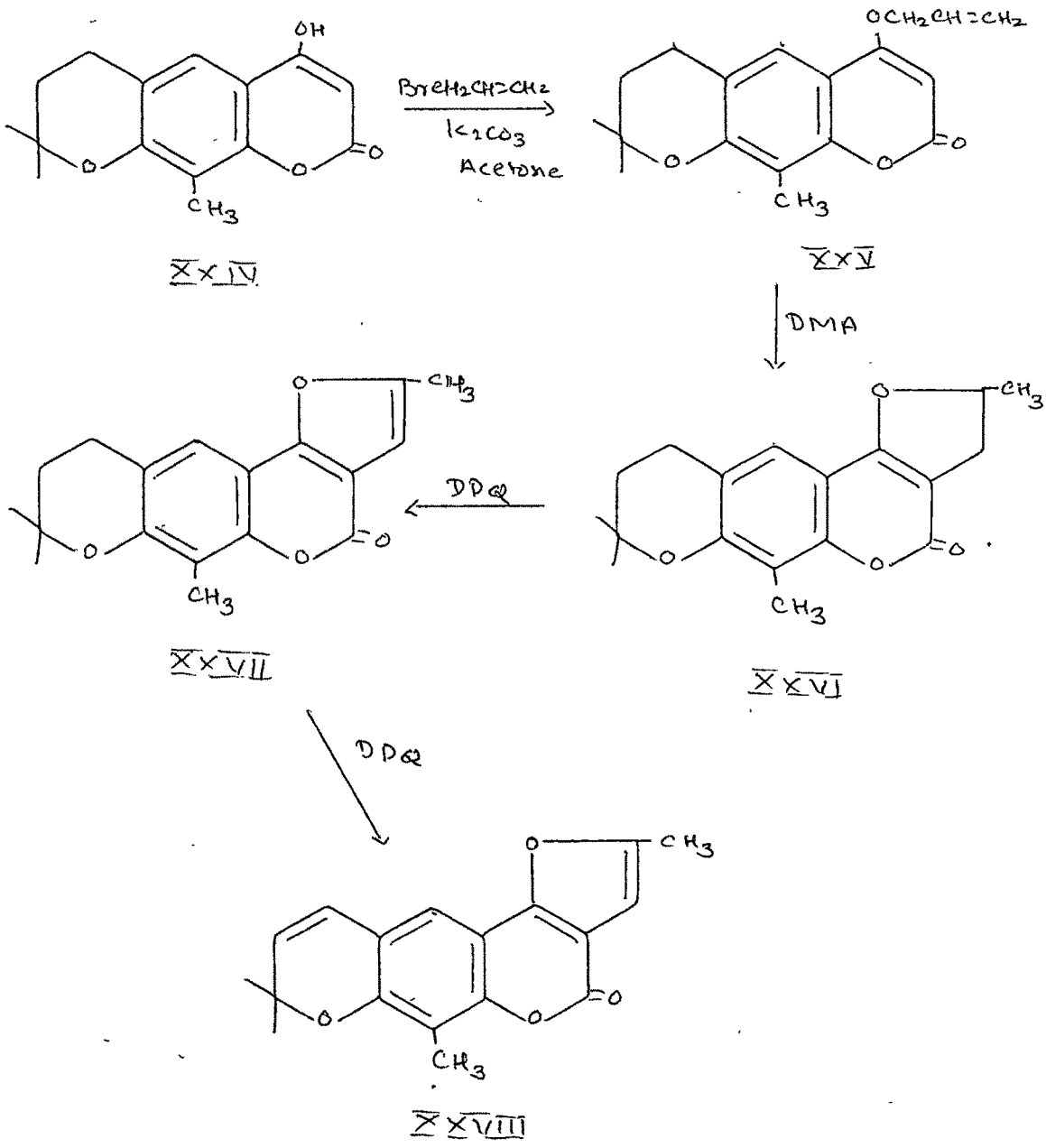
(Fig. 2) : 2,3,9,10-Tetrahydro-2,8,8-trimethyl-4-oxo-4H-furano(3,2-c)-pyrano(3',2'-g)-benzopyran.

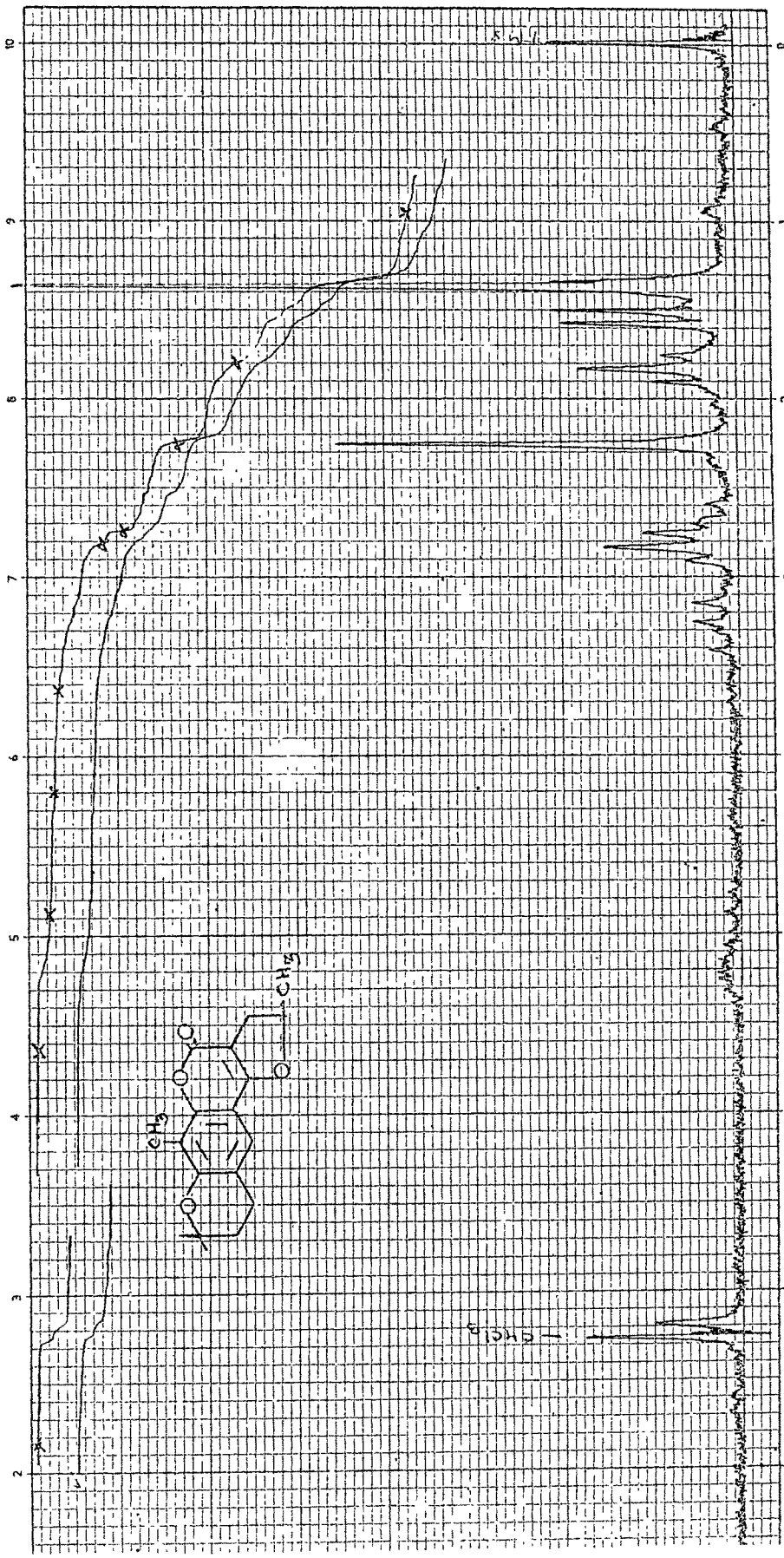
Synthesis of 2,6,8,8-tetramethyl-4-oxo-4H-furano-(3,2-c)pyrano(3',2'-g)benzopyran

3,4-Dihydro-2,2,10-trimethyl-6-hydroxy-8-oxo-8H-pyrano-(3,2-g)benzopyran (XXIV) (prepared according to the method described in Section I) was condensed with allyl bromide in the presence of anhydrous potassium carbonate in acetone to give 3,4-dihydro-2,2,10-trimethyl-6-allyloxy-8-oxo-8H-pyrano(3,2-g)benzopyran (XXV). This on Claisen rearrangement in dimethylaniline gave 2,3,9,10-tetrahydro-2,6,8,8-tetramethyl-4-oxo-4H-furano(3,2-c)pyrano(3',2'-g)benzopyran (XXVI). The NMR spectrum in $CDCl_3$ showed the signals at δ 1.38, singlet, geminal dimethyl group at position-8; 1.55, doublet, J=8Hz, methyl group at position-2; 1.82 and 2.82, two ptriplets, J=7Hz, two methylene groups at positions-9 and -10; 2.25, singlet, methyl group at position-6; 3.25, multiplet, methylene group at position-3; 5.20, multiplet, one proton at position-2- and 7.20, singlet, one proton aromatic at position-11. (Fig. 3)

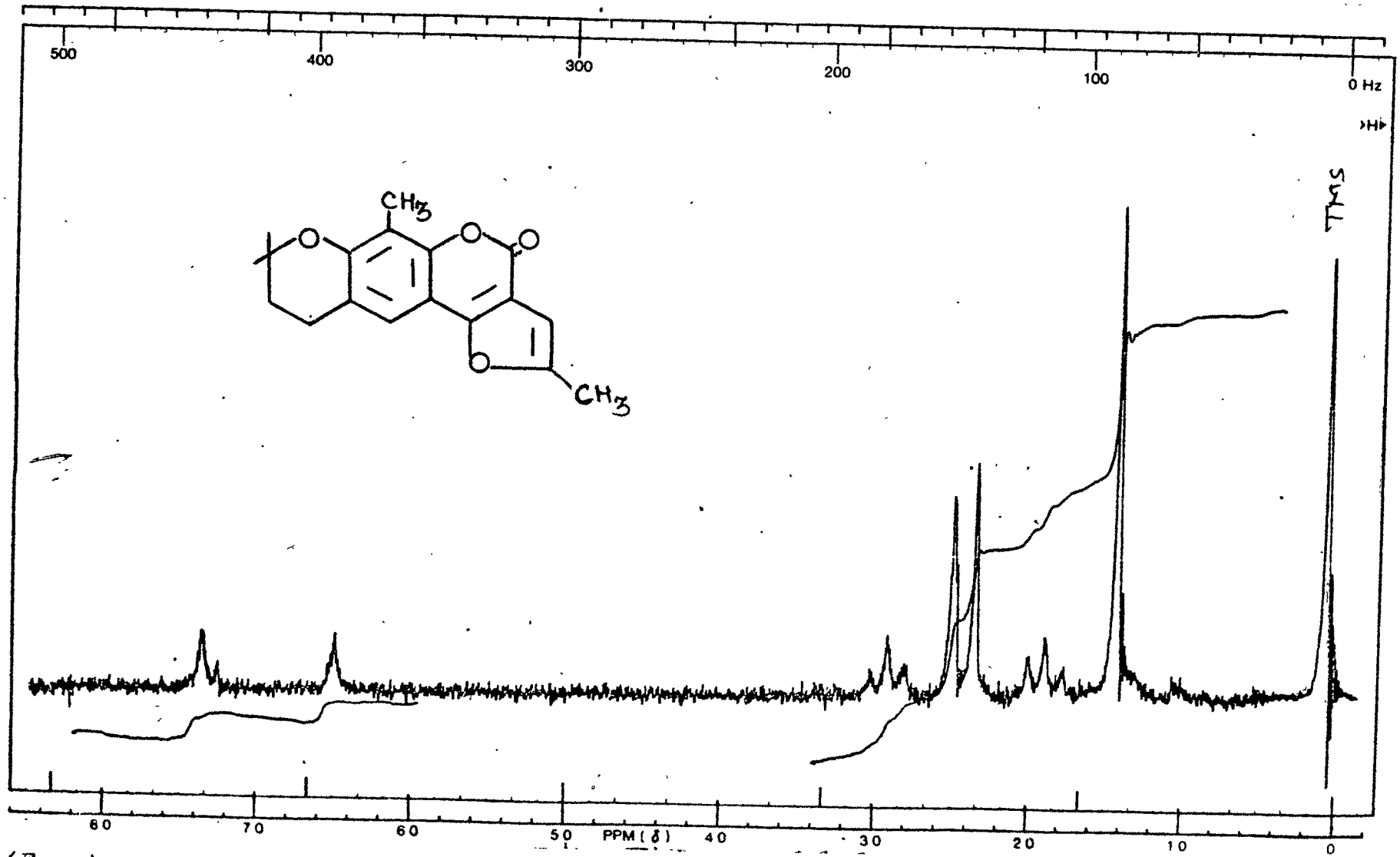
This (XXVI) on refluxing with DDQ in dry benzene gave 9,10-dihydro-2,6,8,8-tetramethyl-4-oxo-4H-furano(3,2-c)-pyrano(3',2'-g)benzopyran (XXVII). The NMR spectrum showed the signals at δ 1.50, singlets, geminal dimethyl group at position-8; 1.90 and 2.98, two triplets, J=7Hz, two methylene group at positions-9 and -10; 2.40, singlet, methyl group at position-6; 2.50, singlet, methyl group at position-2; 6.50, singlet, one proton at position-3 and 7.35, singlet, one

proton aromatic. (Fig.4). (XXVII) on further refluxion with DDQ in dry benzene gave 2,6,8,8-tetramethyl-4-oxo-4H-furano(3,2-c)pyrano(3',2'-g)benzopyran (XXVIII), which showed two doublets at δ 5.45 and 6.55 having coupling constant J=10Hz for two protons at positions-9 and -10.





(Fig. 3) : 2,3,9,10-Tetrahydro-2,6,8,8-tetramethyl-4-oxo-4H-furano(3,2-c)pyrano(3',2'-g)-benzopyran.

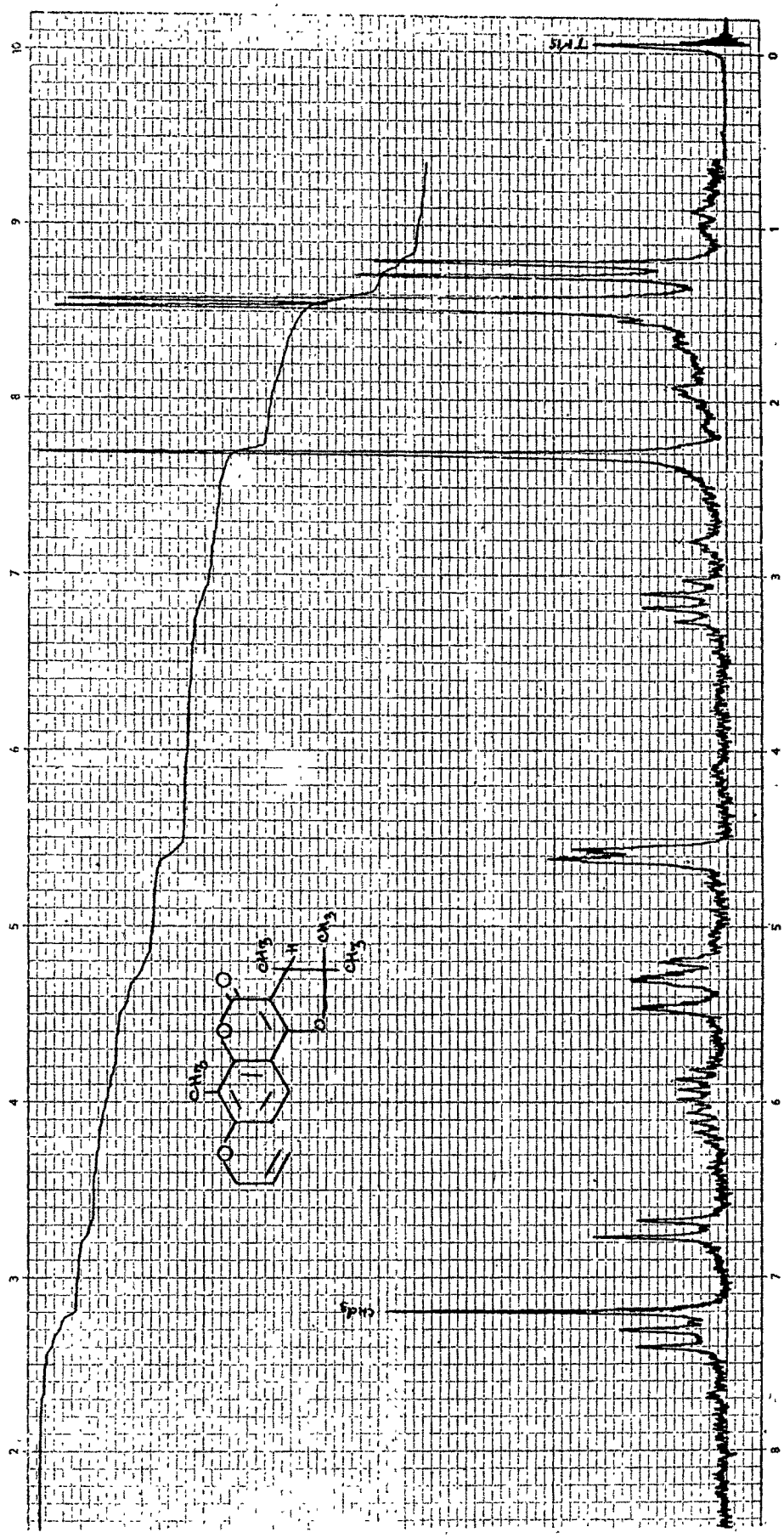


(Fig. 4) : 9,10-Dihydro-2,6,8,8-tetramethyl-4-oxo-4H-furano(3,2-c)pyrano(3',2'-g)benzopyran

Synthesis of 2,3-dihydro-4-oxo-4H-2,2,3,6,8-pentamethyl--difurano(3,2-c : 3',2'-g)benzopyran

7-Allyloxy-4-hydroxy-8-methylcoumarin (XXIX) was prepared according to Dholakia and Trivedi[3]. This was condensed with 1-chloro-3-methyl-but-2-ene in the presence of anhydrous potassium carbonate and potassium iodide in acetone to give 7-allyloxy-8-methyl-4-prenyloxycoumarin (XXX). This on boiling with dimethylaniline gave 2,3-dihydro--7-allyloxy-4-oxo-4H-2,2,3,6-tetramethylfurano(3,2-c)benzo--pyran (XXXI) and 2,3-dihydro-7-hydroxy-8-allyl-4-oxo-4H-2,2,3,6-tetramethylfurano(3,2-c)benzopyran (XXXII). The IR spectrum of (XXXI) in nujol showed the bands at 1720 $cm.^{-1}$ (α-pyrone carbonyl stretching frequency), 1620 $cm.^{-1}$ (aromatic C=C stretching frequency), 1280 $cm.^{-1}$ (>C-O stretching frequency) and 900 $cm.^{-1}$ (allylic >C=C stretching frequency). The NMR spectrum in $CDCl_3$ showed the signals, at δ 1.30, doublet, J=8Hz, methyl group at position-3; 1.38 and 1.42, two singlets, geminal dimethyl group at position-2; 2.25, singlet, methyl group at position-6; 3.10, quartate, J=8Hz, one proton at position-3; 4.55, doublet, two protons of $-\underline{CH_2}-CH=$; 5.15-5.40, triplet, one proton of $-CH_2-\underline{CH}=$; 6.70 and 7.30, two doublets, J=9Hz, two protons aromatic at positions-8 and -9. (Fig.5)

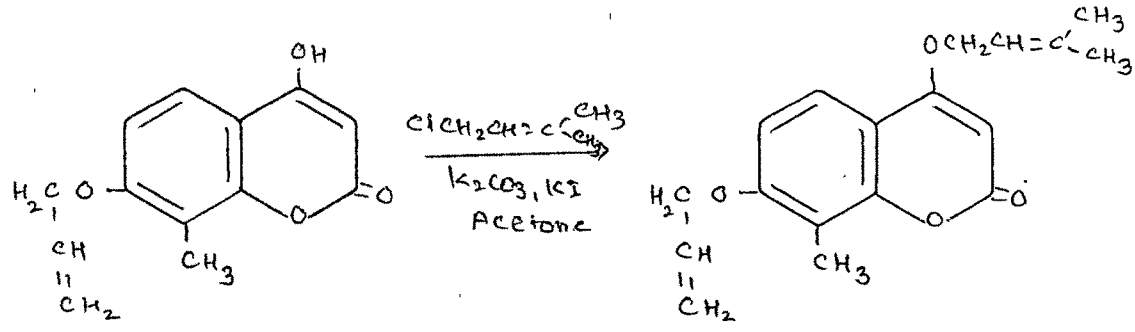
The IR spectrum of (XXXII) showed the bands at 3200 $cm.^{-1}$ (broad), for hydroxyl group, 1695 $cm.^{-1}$ for



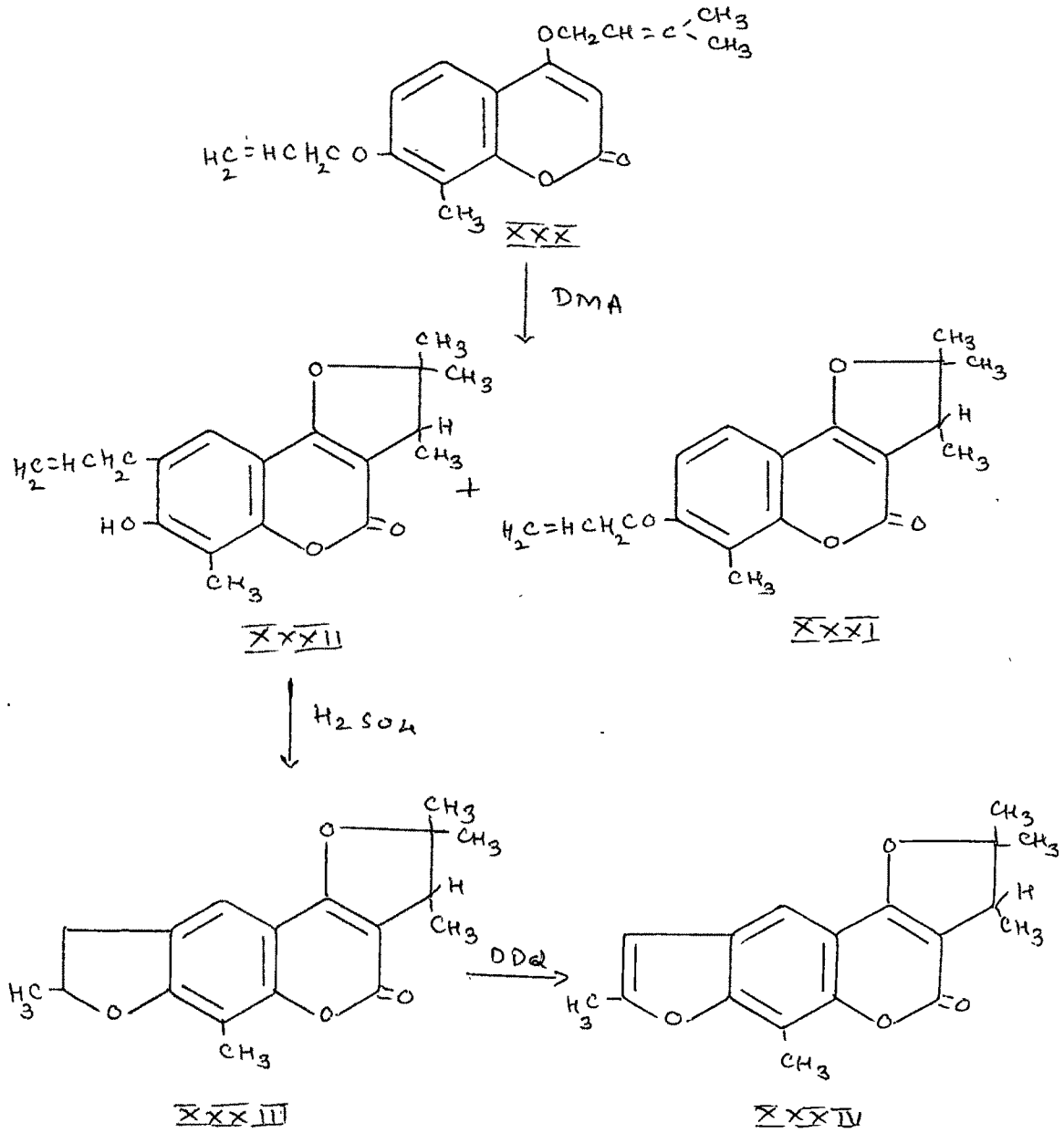
(Fig.5) : 2,3-Dihydro-7-allyloxy-4-oxo-4H-2,3,6-tetramethylfurano(3,2-c)benzopyran

α-pyrone carbonyl stretching frequency, 1370 $cm.^{-1}$ for geminal dimethyl group, 1270 $cm.^{-1}$ for -C-O-C- stretching frequency and 930 $cm.^{-1}$ for allylic -C=C- stretching frequency.

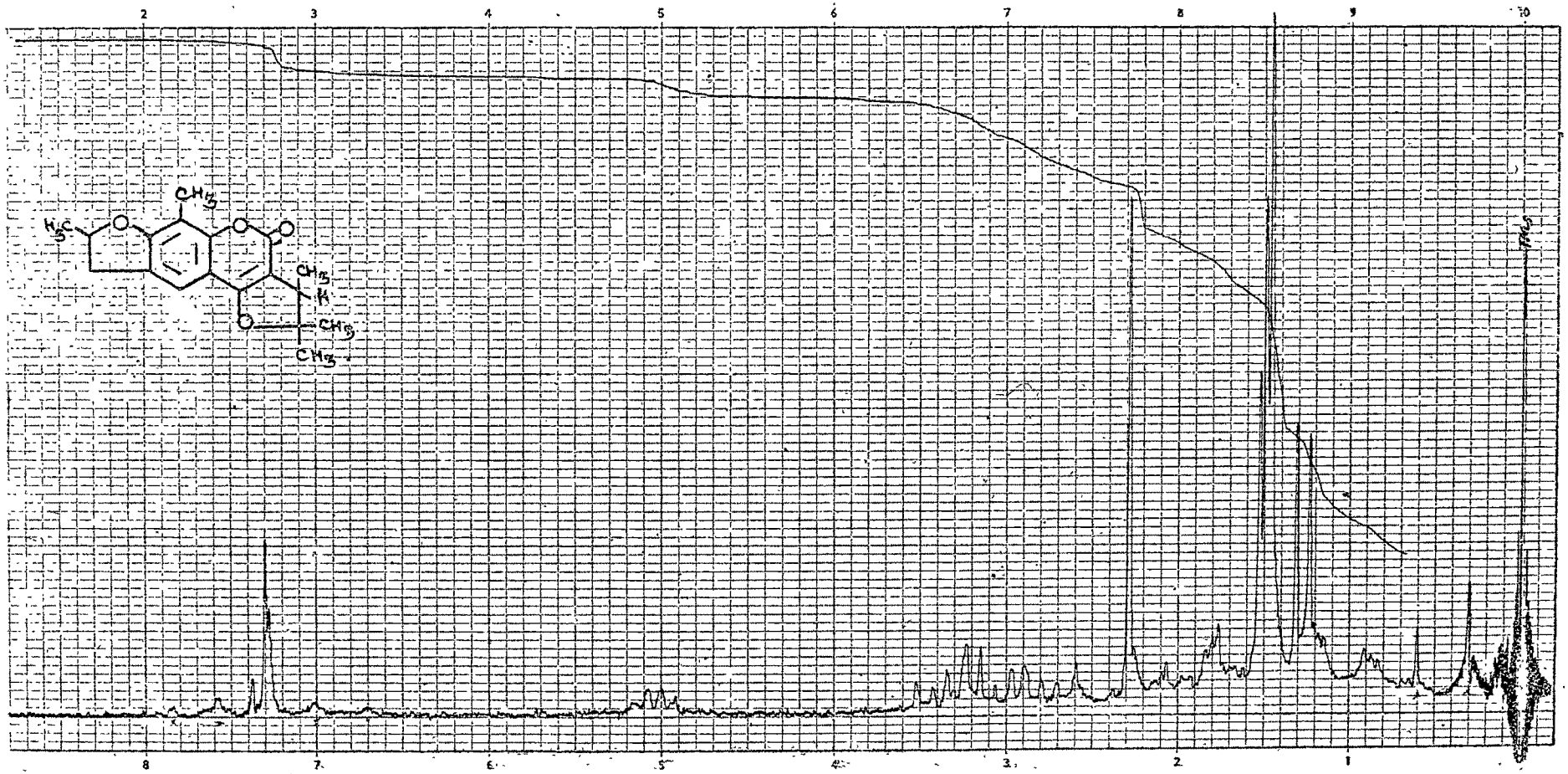
(XXXII) was cyclised by heating with sulphuric acid (84 %) to 2,3,8,9-tetrahydro-4-oxo-4H-2,2,3,6,8-pentamethyldifurano(3,2-c : 3',2'-g)benzopyran (XXXIII). The IR spectrum in nujol showed the bands at 1705 $cm.^{-1}$ (α-pyrone carbonyl stretching frequency) and 970 $cm.^{-1}$ (furan ring). The NMR spectrum of (XXXIII) in $CDCl_3$ showed the signals at δ 1.30, doublet, J=8Hz, methyl group at position-3; 1.48 and 1.50, two singlets, geminal dimethyl group at position-2; 1.50, doublet, methyl group at position-8; 2.28, singlet, methyl group at position-6; 2.75, quartate, one proton at position-3; 2.97-3.50, multiplet, two protons at position-9; 5.00, quartate, one proton at position-8 and 7.30, one proton aromatic at position-11. (Fig.6)



XXIX XXX



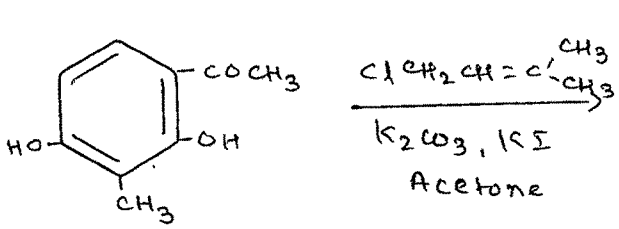
(XXXIII) was further refluxed with DDQ in benzene to give 2,3-dihydro-4-oxo-4H-2,2,3,6,8-pentamethyldifurano-(3,2-c : 3',2'-g)benzopyran (XXXIV). The NMR spectrum showed a doublet at δ 2.55, for a methyl group at position -8 and a signal at δ 5.05, as quartate, for one proton at position-9.



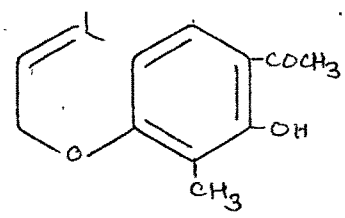
(Fig.6) : 2,3,8,9-Tetrahydro-4-oxo-4H-2,2,3,6,8-pentamethyldifurano(3,2-c : 3',2'-g)benzopyran

Synthesis of 2,3-dihydro-4-oxo-4H-7-hydroxy-2,6-dimethyl--8-prenylfurano(3,2-c)benzopyran

2,4-Dihydroxy-3-methylacetophenone (XXXV) was prenylated with 1-chloro-3-methyl-but-2-ene in the presence of anhydrous potassium carbonate and potassium iodide to 4-prenyloxy-2-hydroxy-3-methylacetophenone (XXXVI). This was further condensed with diethyl carbonate in the presence of pulverised sodium to give 4-hydroxy-8-methyl-7-prenyloxy-coumarin (XXXVII). This was refluxed with allyl bromide in the presence of anhydrous potassium carbonate in acetone to obtain 4-allyloxy-8-methyl-7-prenyloxycoumarin (XXXVIII). The IR spectrum in nujol showed the bands at 1700 $cm.^{-1}$ (α-pyrone carbonyl stretching frequency) and 920 $cm.^{-1}$ (allylic C=C stretching frequency). This on refluxing with dimethylaniline gave 2,3-dihydro-4-oxo-4H-7-hydroxy-2,6-dimethyl-8-prenyl-furano(3,2-c)benzopyran (XXXIX). The corresponding cyclised or dehydrogenated product could not be obtained by the usual methods. The NMR spectrum of (XXXIX) in $CDCl_3$ showed the signals at δ 1.50, doublet, methyl group at position-2; 1.60 and 1.70, two singlets, geminal dimethyl group; 2.40, singlet, methyl group at position-6; 2.60-2.80, multiplet, methylene group at position-3 and two protons of $-C\underline{H}_2-CH=$ group; 5.20, triplet, (broad), two protons, $-CH_2-C\underline{H}$ group and -OH group, 6.50, singlet, one proton at position-2 and 7.40, singlet, one proton aromatic at position-9. (Fig.7)

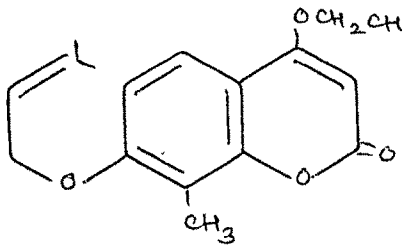


XXXV

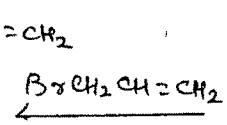


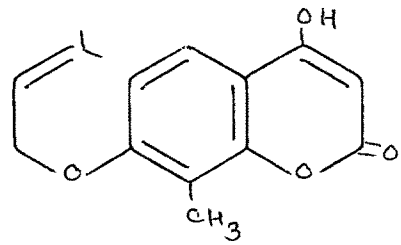
XXXVI

Na,
Diethyl carbonate



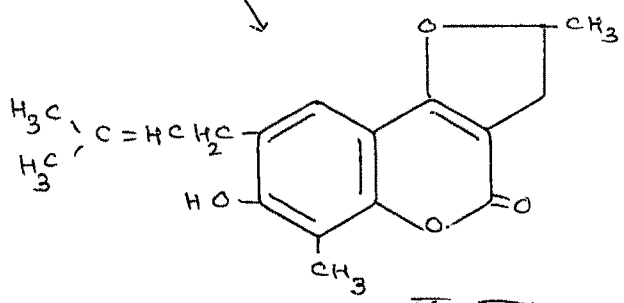
XXXVIII



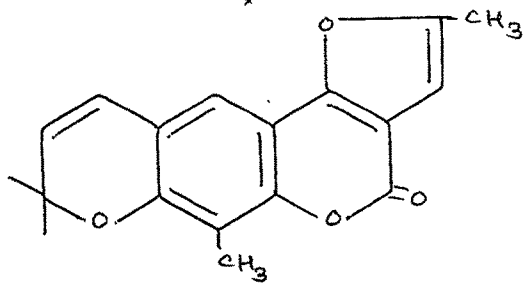


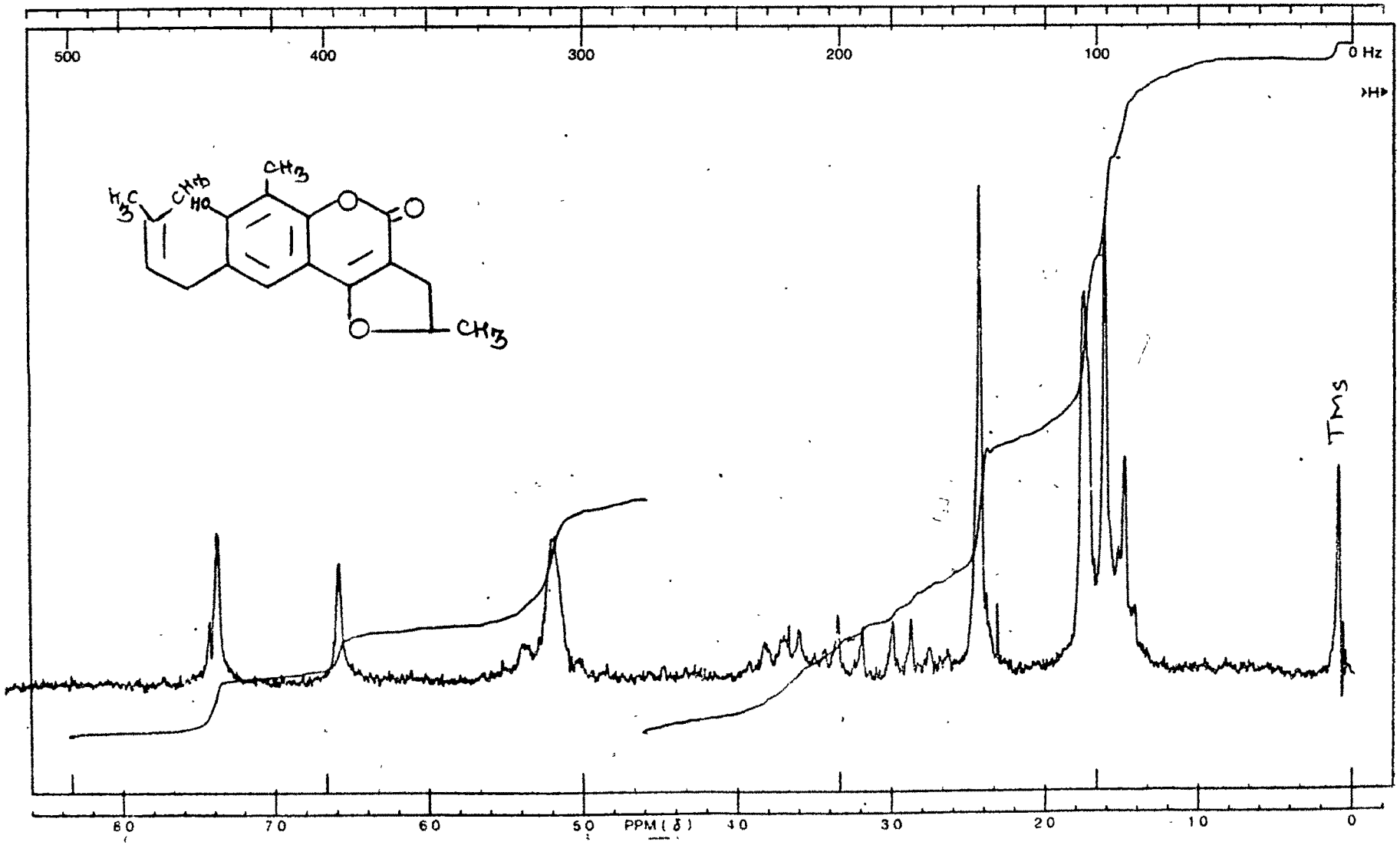
XXXVII

DMA



XXXIX





(Fig.7) : 2,3-Dihydro-4-oxo-4H-7-hydroxy-2,6-dimethyl-8-prenylfurano(3,2-c)benzopyran

EXPERIMENTAL

2,8,8-Trimethyl-4-oxo-4H-furano(3,2-c)pyrano(2',3'-h)benzopyran (X) : 8-Allyloxy-3,4-dihydro-2,2-dimethyl-6-oxo--6H-pyrano(2,3-h)benzopyran (VIII) :

3,4-Dihydro-2,2-dimethyl-8-hydroxy-6-oxo-6H-pyrano(2,3-h)benzopyran (0.8 g.), anhydrous potassium carbonate (2.0 g.) and allyl bromide (0.5 g.) were refluxed in acetone (50 ml.) for 10 hr. The solvent was removed by distillation and the residue was diluted with water. The whole solution was then extracted with ether. A semi solid mass was obtained on evaporating the ether which on passing through alumina and eluting with benzene gave a solid, 8-allyloxy-3,4-dihydro-2,2-dimethyl-6-oxo-6H-pyrano(2,3-h)-benzopyran, crystallised from benzene-petroleum ether, m.p. 150-51°. Yield 0.4 g.

Analysis : Found : C, 70.89 ; H, 6.65 %

$C_{17}H_{18}O_4$ requires : C, 71.32 ; H, 6.29 %.

Claisen migration of 8-allyloxy-3,4-dihydro-2,2-dimethyl--6-oxo-6H-pyrano(2,3-h)benzopyran : 2,3,6,7-Tetrahydro--2,8,8-trimethyl-4-oxo-4H-furano(3,2-c)pyrano(2',3'-h)--benzopyran (IX) :

8-Allyloxy-3,4-dihydro-2,2-dimethyl-6-oxo-6H--pyrano(2,3-h)benzopyran (0.3 g.) was refluxed with dimethyl-aniline (5 ml.) for 2 hr. The solution was cooled and poured into the dilute hydrochloric acid solution. The solid

separated was filtered, washed with water and crystallised from benzene-petroleum ether, as 2,3,6,7-tetrahydro-2,8,8--trimethyl-4-oxo-4H-furano(3,2-c)pyrano(2',3'-h)benzopyran, m.p. 190°. Yield 0.15 g.

Analysis : Found : C, 70.88 ; H, 5.89 %

$C_{17}H_{18}O_4$ requires : C, 71.32 ; H, 6.29 %.

2,3-Dihydro-2,8,8-trimethyl-4-oxo-4H-furano(3,2-c)pyrano--(2',3'-h)benzopyran (XII) :

2,2-Dimethyl-8-hydroxy-6-oxo-6H-pyrano(2',3'-h)-benzopyran (0.5 g.) was refluxed with allyl bromide (0.3 g.) and anhydrous potassium carbonate (1.5 g.) in acetone (50 ml.) for 8 hr. The solvent was removed by distillation and the residue was diluted with water. The product obtained was directly refluxed with dimethylaniline (2 ml.) for 4 hr. The reaction mixture was poured into the dilute hydrochloric acid solution. The solid obtained was filtered and washed with dilute sodium hydroxide solution and crystallised from benzene-petroleum ether mixture to give 2,3-dihydro-2,8,8,--trimethyl-4-oxo-4H-furano(3,2-c)pyrano(2',3'-h)benzopyran, m.p. 140-42°. Yield 0.20 g.

Analysis : Found : C, 71.33 ; H, 6.22 %

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

4-Hydroxy-7-prenyloxycoumarin (XV) :

2-Hydroxy-4-prenyloxyacetophenone (5.0 g.), diethyl carbonate (20 ml.) and pulverised sodium (4.0 g.)

were heated on a water bath for 12 hr. Alcohol (50 ml.) was added to the reaction mixture to decompose the unreacted sodium and the whole solution was added to the ice-cold water. The solution was then extracted with ether and aqueous solution on acidification with hydrochloric acid gave a solid, 4-hydroxy-7-prenyloxycoumarin, crystallised from alcohol, m.p. 183-84°. Yield 0.3 g.

Analysis : Found : C, 68.80 ; H, 5.71 %

$C_{14}H_{14}O_4$ requires : C, 68.30 ; H, 5.79 %.

4-Allyloxy-7-prenyloxycoumarin (XVI) :

A mixture of 4-hydroxy-7-prenyloxycoumarin (1.0 g.), anhydrous potassium carbonate (3.0 g.) and allyl bromide (0.5 g.) was refluxed in acetone (50 ml.) on a water bath for 12 hr. The solvent was evaporated and water was added to the residue. The whole solution was extracted with ether and the residue obtained after the evaporation of ether, crystallised from petroleum ether, as 4-allyloxy-7-prenyloxy--coumarin, m.p. 80-2°. Yield 0.2 g.

Analysis : Found : C, 71.25 ; H, 6.29 %

$C_{17}H_{18}O_4$ requires : C, 71.32 ; H, 6.29 %.

Claisen migration of 4-allyloxy-7-prenyloxycoumarin : 2,3-Dihydro-2-methyl-7-prenyloxy-4-oxo-4H-furano(3,2-c)--benzopyran (XVII) :

4-Allyloxy-7-prenyloxycoumarin (0.15 g.) was refluxed with dimethylaniline (3 ml.) for 2 hr. The solution

was added to the dilute hydrochloric acid solution and the solid obtained was filtered and crystallised from benzene-petroleum ether mixture to give 2,3-dihydro-2-methyl-7-prenyloxy--4-oxo-4H-furano(3,2-c)benzopyran, m.p. 126-27°. Yield 0.05 g.

Analysis : Found : C, 71.52 ; H, 5.91 %

$C_{17}H_{18}O_4$ requires : C, 71.32 ; H, 6.29 %.

This on prolonged refluxion with dimethylaniline gave 2,3,6,7-tetrahydro-2,8,8-trimethyl-4-oxo-4H-furano--(3,2-c)pyrano(2',3'-h)benzopyran, m.p. 188°. The mixed m.p. of this compound did not depress with the compound prepared earlier.

2,8,8-Trimethyl-4-oxo-4H-furano(3,2-c)pyrano(3',2'-g)-benzopyran (XXI) : 6-Allyloxy-3,4-dihydro-2,2-dimethyl--8-oxo-8H-pyrano(3,2-g)benzopyran (XIX) :

3,4-Dihydro-2,2-dimethyl-6-hydroxy-8-oxo-8H--pyrano(3,2-g)benzopyran (0.8 g.), anhydrous potassium carbonate (2.0 g.) and allyl bromide (0.5 g.) were refluxed in acetone (50 ml.) for 10 hr. The solvent was evaporated and the water was added to the residue. The solution was extracted with ether and the ether layer on evaporation gave a residue which gave a solid on passing through alumina, was crystallised from benzene-petroleum ether mixture to give 6-allyloxy-3,4-dihydro-2,2-dimethyl-8-oxo-8H-pyrano-(3,2-g)benzopyran, m.p. 140-42°. Yield 0.5 g.

Analysis : Found : C, 71.77 ; H, 6.32 %

$C_{17}H_{18}O_4$ requires : C, 71.32 ; H, 6.29 %.

Claisen migration of 6-allyloxy-3,4-dihydro-2,2-dimethyl--8-oxo-8H-pyrano(3,2-g)benzopyran : 2,3,9,10-Tetrahydro--2,8,8-trimethyl-4-oxo-4H-furano(3,2-c)pyrano(3',2'-g)-benzopyran (XX) :

6-Allyloxy-3,4-dihydro-2,2-dimethyl-8-oxo-8H-pyrano(3,2-g)benzopyran (0.2 g.) was refluxed with dimethylaniline (5 ml.) for 2 hr. The mixture was poured into dilute hydrochloric acid solution. The solid separated was filtered and washed and crystallised from benzene-petroleum ether mixture, m.p. 191-92°. Yield 0.1 g.

Analysis : Found : C, 71.41 ; H, 6.46 %

$C_{17}H_{18}O_4$ requires : C, 71.32 ; H, 6.29 %.

2,6,8,8-Tetramethyl-4-oxo-4H-furano(3,2-c)pyrano(3',2'-g)--benzopyran (XXVIII) : 3,4-Dihydro-2,2,10-trimethyl--6-allyloxy-8-oxo-8H-pyrano(3,2-g)benzopyran (XXV) :

3,4-Dihydro-2,2,10-trimethyl-6-hydroxy-8-oxo-8H--pyrano(3,2-g)benzopyran (1.0 g.), anhydrous potassium carbonate (2.0 g.) and allyl bromide (0.5 g.) were refluxed in acetone (50 ml.) on a water bath for 10 hr. The solvent was removed by distillation and the residue was extracted with ether. The ether layer was washed with water and the residue, obtained after evaporation of the solvent, was, crystallised from petroleum ether to give 3,4-dihydro-2,2,10-trimethyl-6-allyloxy-8-oxo-8H-pyrano(3,2-g)benzopyran, m.p. 171-72°. Yield 0.6 g.

Analysis : Found : C, 72.41 ; H, 6.59 %

$C_{18}H_{20}O_4$ requires : C, 72.00 ; H, 6.66 %.

Claisen migration of 3,4-dihydro-2,2,10-trimethyl-6-allyloxy--8-oxo-8H-pyrano(3,2-g)benzopyran : 2,3,9,10-Tetrahydro--2,6,8,8-tetramethyl-4-oxo-4H-furano(3,2-c)pyrano(3',2'-g)--benzopyran (XXVI) :

3,4-Dihydro-2,2,10-trimethyl-6-allyloxy-8-oxo-8H--pyrano(3,2-g)benzopyran (0.5 g.) was refluxed with dimethyl-aniline (5 ml.) for 2 hr. The solution was cooled and poured into the dilute hydrochloric acid solution. The solid separated was filtered and crystallised from benzene-petroleum ether mixture to give 2,3,9,10-tetrahydro-2,6,8,8-tetramethyl-4--oxo-4H-furano(3,2-c)pyrano(3',2'-g)benzopyran, m.p. 140-42°. Yield 0.3 g.

Analysis : Found : C, 72.36 ; H, 6.61 %

$C_{18}H_{20}O_4$ requires : C, 72.00 ; H, 6.66 %.

9,10-Dihydro-2,6,8,8-tetramethyl-4-oxo-4H-furano(3,2-c)--pyrano(3',2'-g)benzopyran (XXVII) :

2,3,9,10-Tetrahydro-2,6,8,8-tetramethyl-4-oxo--4H-furano(3,2-c)pyrano(3',2'-g)benzopyran (0.2 g.) was refluxed in dry benzene with DDQ (0.2 g.) for 40 hr. The solid separated was filtered hot and washed with hot benzene. The filtrate was concentrated and the residue on column chromatography over silica gel gave a solid, 9,10-dihydro-2,6,8,8-tetramethyl-4-oxo-4H-furano(3,2-c)-pyrano(3',2'-g)-

benzopyran crystallised from benzene-petroleum ether mixture, m.p. 159-60°. Yield 0.15 g.

Analysis of this product did not agree with the molecular formulae, but the structure was confirmed on the basis of its NMR spectrum.

2,6,8,8-Tetramethyl-4-oxo-4H-furano(3,2-c)pyrano(3',2'-g)-benzopyran (XXVIII) :

9,10-Dihydro-2,6,8,8-tetramethyl-4-oxo-4H-furano-(3,2-c)pyrano(3',2'-g)benzopyran (0.1 g.) was refluxed with DDQ (0.1 g.) in dry benzene (10 ml.) for 70 hr. The solid separated was filtered hot and washed with benzene. The filtrate was concentrated and the residue was eluted with benzene over the column of silica gel. The solid, 2,6,8,8-tetramethyl-4-oxo-4H-furano(3,2-c)pyrano(3',2'-g)benzopyran, crystallised from benzene-petroleum ether mixture, m.p. 177-78°. Yield 0.03 g.

Analysis : Found : C, 72.64 ; H, 6.26 %

$C_{18}H_{16}O_4$ requires : C, 72.97 ; H, 5.40 %.

2,3-Dihydro-4-oxo-4H-2,2,3,6,8-pentamethyldifurano(3,2-c : 3',2'-g)benzopyran (XXXIV) : 7-Allyloxy-8-methyl-4-prenyl-oxycoumarin (XXX) :

4-Allyloxy-3-methyl-2-hydroxyacetophenone (5.0 g.) was heated on a water bath with diethyl carbonate (15 ml.) and pulverised sodium (5.0 g.) for 10 hr. The mixture was added to the cold water and the solution was filtered. The

alkaline filtrate was acidified with dilute hydrochloric acid to give 4-hydroxy-7-allyloxy-8-methylcoumarin (2.0 g.) which was further refluxed with 1-chloro-3-methyl-but-2-ene (2 ml.), anhydrous potassium carbonate (6.0 g.) and potassium iodide (1.0 g.) in acetone (50 ml.) on a water bath for 8 hr. The solvent was removed by distillation and water was added to the residue. The solid separated was filtered and crystallised from benzene-petroleum ether mixture to give 7-allyloxy-8-methyl-4-prenyloxycoumarin, m.p. 142-44°. Yield 1.0 g.

Analysis : Found : C, 72.16 ; H, 6.60 %

$C_{18}H_{20}O_4$ requires : C, 72.00 ; H, 6.66 %.

Claisen migration of 7-allyloxy-8-methyl-4-prenyloxycoumarin : 7-Allyloxy-2,3-dihydro-4-oxo-4H-2,2,3,6-tetramethylfurano--(3,2-c)benzopyran (XXXI) : and 8-allyl-2,3-dihydro-7-hydroxy-4-oxo-4H-2,2,3,6-tetramethylfurano(3,2-c)benzopyran (XXXII) :

7-Allyloxy-8-methyl-4-prenyloxycoumarin (0.8 g.) was refluxed with dimethylaniline (5 ml.) for 3 hr. The solution was added to dilute hydrochloric acid solution and extracted with ether. The ether layer was washed with dilute sodium hydroxide solution which on acidification gave a solid, 8-allyl-7-hydroxy-2,3-dihydro-4-oxo-4H-2,2,3,6-tetramethyl-furano(3,2-c)benzopyran, crystallised from benzene-petroleum ether mixture, m.p. 180-81°. Yield 0.4 g.

Analysis : Found : C, 72.46 ; H, 6.52 %

$C_{18}H_{20}O_4$ requires : C, 72.00 ; H, 6.66 %.

The ether layer on evaporation gave a solid, 7-allyloxy-2,3-dihydro-4-oxo-4H-2,2,3,6-tetramethylfurano-(3,2-c)benzopyran, crystallised from petroleum ether, m.p. 105-6°. Yield 0.1 g.

Analysis : Found : C, 72.11 ; H, 6.59 %

$C_{18}H_{20}O_4$ requires : C, 72.00 ; H, 6.66 %.

2,3,8,9-Tetrahydro-4-oxo-4H-2,2,3,6,8-pentamethyldifurano-(3,2-c:3',2'-g)benzopyran (XXXIII) :

8-Allyl-7-hydroxy-2,3-dihydro-4-oxo-4H-2,2,3,6-tetramethylfurano(3,2-c)benzopyran (0.3 g.) was heated with sulphuric acid (84 % ; 5 ml.) on a water bath for 15 minutes. The solution was added to the cold water and the solid separated was filtered and crystallised from benzene-petroleum ether mixture to give 2,3,8,9-tetrahydro-4-oxo-4H-2,2,3,6,8-pentamethyldifurano(3,2-c : 3',2'-g)benzopyran, m.p. 188-89°. Yield 0.2 g.

Analysis : Found : C, 72.43 ; H, 6.44 %

$C_{18}H_{20}O_4$ requires : C, 72.00 ; H, 6.66 %.

2,3-Dihydro-4-oxo-4H-2,2,3,6,8-pentamethyldifurano(3,2-c : 3',2'-g)benzopyran (XXXIV) :

2,3,8,9-Tetrahydro-4-oxo-4H-2,2,3,6,8-pentamethyldifurano(3,2-c : 3',2'-g)benzopyran (0.15 g.) was refluxed with DDQ (0.15 g.) in dry benzene (10 ml.) for 24 hr.

The solution was filtered hot and the residue washed with hot benzene. The solvent was evaporated and the residue was chromatographed over silica gel. Elution with benzene gave a product, 2,3-dihydro-4-oxo-4H-2,2,3,6,8-pentamethyldifurano-(3,2-c : 3',2'-g)benzopyran, crystallised from benzene-petroleum ether mixture, m.p. 182-83°. Yield 0.07 g.

Analysis : Found : C, 72.23 ; H, 5.85 %

$C_{18}H_{18}O_4$ requires : C, 72.48 ; H, 6.02 %.

2,3-Dihydro-4-oxo-4H-7-hydroxy-2,6-dimethyl-8-prenylfurano--(3,2-c)benzopyran (XXXIX) : 2-Hydroxy-3-methyl-4-prenyloxy--acetophenone (XXXVI) :

2,4-Dihydroxy-3-methylacetophenone (5.0 g.), anhydrous potassium carbonate (15.0 g.), potassium iodide (2.0 g.) and 1-chloro-3-methyl-but-2-ene (6 ml.) were refluxed in acetone (100 ml.) for 3 hr. on a water bath. The solvent was evaporated and the residue was diluted with water. The solution was then extracted with ether. The ether layer on evaporation gave a solid, 2-hydroxy-3-methyl-4-prenyloxy-acetophenone, crystallised from petroleum ether, m.p. 70°. Yield 4.0 g.

Analysis : Found : C, 70.86 ; H, 7.70 %

$C_{14}H_{18}O_3$ requires : C, 70.59 ; H, 7.56 %.

4-Hydroxy-8-methyl-7-prenyloxycoumarin (XXXVII) :

2-Hydroxy-3-methyl-4-prenyloxyacetophenone (4.0 g.) was dissolved in diethyl carbonate (10 ml.) and the solution

was added to the pulverised sodium (4.0 g.). The whole mixture was then heated on a water bath for 10 hr. The excess of sodium was destroyed by the addition of alcohol (10 ml.) and the mixture was added to the cold water. The solution was filtered and the filtrate, on acidification, gave a solid, 4-hydroxy-8-methyl-7-prenyloxycoumarin, crystallised from ethyl acetate-petroleum ether mixture, m.p. 184-86°. Yield 4.0 g.

4-Allyloxy-8-methyl-7-prenyloxycoumarin (XXXVIII) :

A mixture of 4-hydroxy-8-methyl-7-prenyloxy-coumarin (2.0 g.), anhydrous potassium carbonate (5.0 g.) and allyl bromide (1.5 ml.) in acetone (100 ml.) was refluxed on a water bath for 6 hr. The solvent was evaporated and water was added to the residue. The solid separated was filtered and crystallised from benzene-petroleum ether mixture to give 4-allyloxy-8-methyl-7-prenyloxycoumarin, m.p. 146-48°. Yield 1.5 g.

Analysis : Found : C, 72.21 ; H, 6.59 %

$C_{18}H_{20}O_4$ requires : C, 72.00 ; H, 6.66 %.

Claisen migration of 4-allyloxy-8-methyl-7-prenyloxycoumarin : 2,3-Dihydro-4-oxo-4H-7-hydroxy-2,6-dimethyl-8-prenylfurano--(3,2-c)benzopyran (XXXIX) :

4-Allyloxy-8-methyl-7-prenyloxycoumarin (1.0 g.) was refluxed with dimethylaniline (10 ml.) for 6 hr. The solution was added to the dilute hydrochloric acid solution and the whole solution was extracted with ether. The ethereal

layer was first extracted with sodium bicarbonate solution (10 %)which on acidification gave a trace of 4-hydroxy-coumarin derivative. It was again washed with dilute sodium hydroxide solution which on acidification gave a solid, 2,3-dihydro-4-oxo-4H-7-hydroxy-2,6-dimethyl-8-prenylfurano--(3,2-c)benzopyran, crystallised from benzene-petroleum ether mixture, m.p. 189-90°. Yield 0.4 g.

Analysis : Found : C, 72.33 ; H, 6.35 %

$C_{18}H_{20}O_4$ requires : C, 72.00 ; H, 6.66 %.

The ethereal solution on evaporation gave 4-allyloxy--8-methyl-7-prenyloxycoumarin.

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