# CHAPTER III.

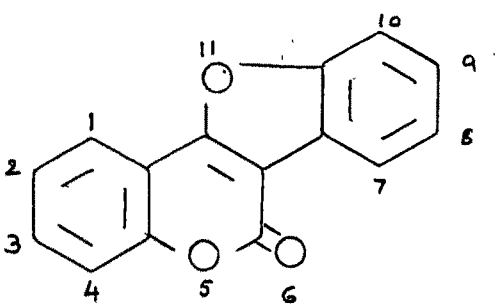
## STUDIES IN THE SYNTHESIS OF FURO-COUMESTAN DERIVATIVES

# CHAPTER III.

## Studies in the synthesis of furocoumestan derivatives.

### THEORETICAL.

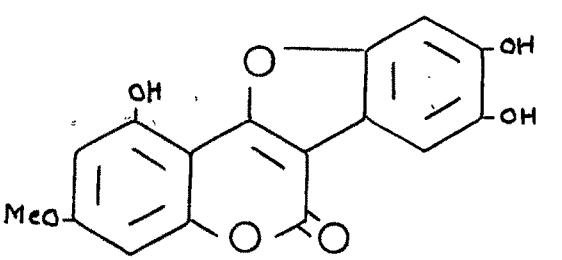
The trivial name Coumestan, has been proposed for the skeletal structure (1) of the heterocyclic four ring system having the systematic name, 6H-benzofuro (3,2-c) [1] - benzopyran-6-one[1].



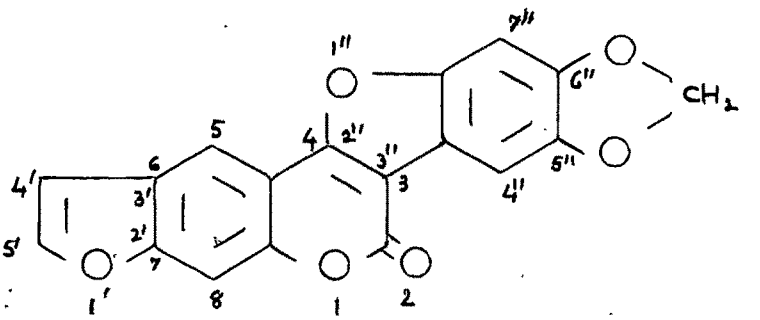

(1)

The names Coumaronocoumarin, benzofurano-a-benzo-pyrone, and coumarino benzofuran have been applied to the class of compounds of which coumestrol (2) is a representative[2]. The list of naturally occuring coumestan is growing and now includes wedelolactone[3,4] (A), erosnin[5] (B), medicagol[6] (C), trifoliol[7] (D), psoralidin[8] (E), sativol[9] (G) and lucernol[9] (F). The coumaronocoumarins are of structural interest in that

They are related to the coumaranochromans and the 3-aryl coumarins. Coumestans are relatively a new class of naturally occuring compounds, identified in a number of plants[3-9]. This class of compound is of particular interest because of coumestrol[10,11,12] found in forage crops[13], possesses estrogenic properties[14] and has a relationship to pathogenic attack of the plant[15]. Coumestrol is the simplest naturally occuring coumestan. It is 3,9-dihydroxycoumestan. The only other known naturally occuring disubstituted coumestan is its 9-methoxy derivative. Trisubstituted coumestan includes sativol[9], lucernol[9], trifoliol[7] and psoralidin[8]. Wedelolactone[3] and norwedelolactone[4] are the only known naturally occuring tetra substituted coumestan derivative.




(A)

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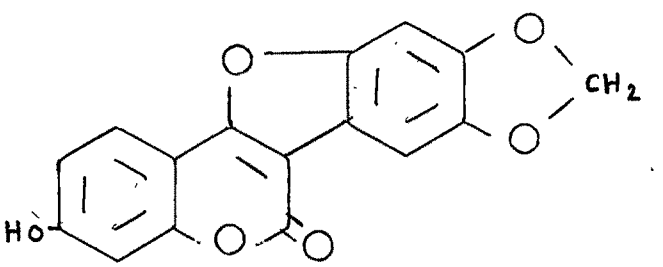
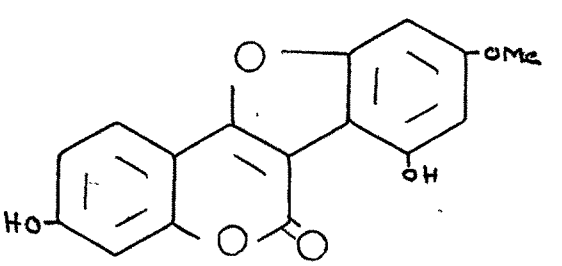
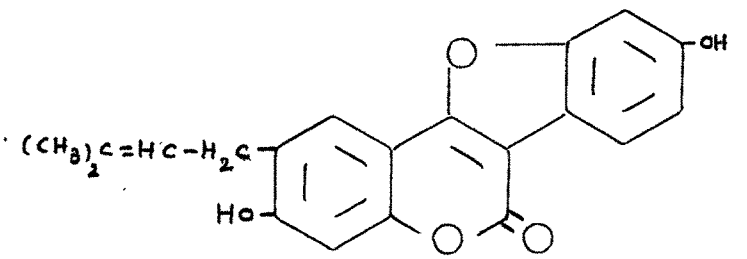


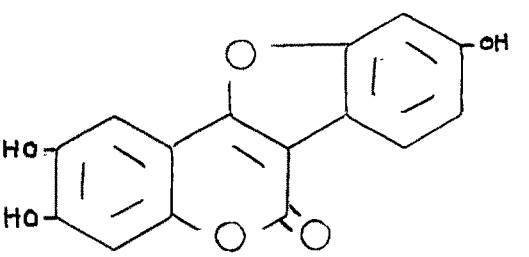

(C)



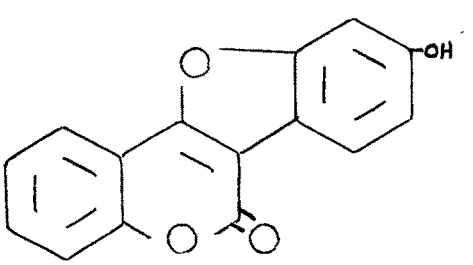

(D)




(E)

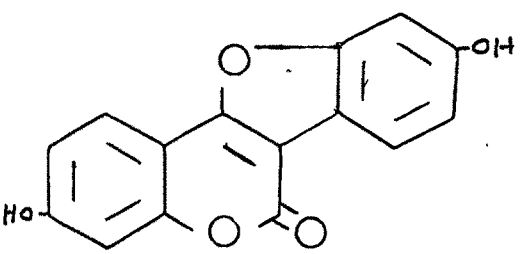



(G)




(F)

A discussion of oestrogenic activity in coumarin-type compounds may include a brief consideration of the closely related isoflavones, which were the first of the plant phenolics to show such activity. The isoflavones, may well be the source of coumarin oestrogens, e.g. coumestrol (2) in the plant.



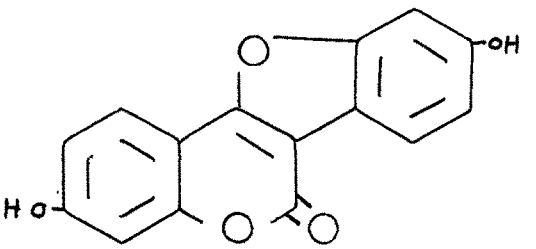

(2)

The matter of oestrogenic activity of plant phenolics was revived when Bickoff and co-workers[11,12] isolated the oestrogenic coumarinocoumarone, coumestrol which was approximately 30 times as potent as genistein, although still far short of diethylstilbestrol[17,18,19]. The relationship of coumestrol structure to its biological activity has been investigated[14,20,21]. A number of co-relation of structure with activity was observed. The phenolic hydroxyl group in position 3 and 9 were quite important, since their absence led to inactivity. Etherification of the phenolic group results in reduced activity.

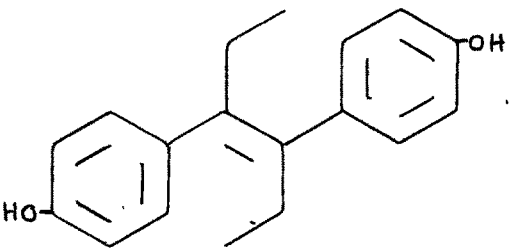
Etherification of hydroxyl group in 9-position reduces activity more than similar treatment of the hydroxyl group in position 3. Acetylation of the hydroxyl group results in a very little loss in activity, possibly due to the hydrolysis of these group in vivo with regeneration of coumestrol. Other nuclear substitution, for example, in 1- and 10-position almost eliminate activity.

The presence of furan ring appears to be an important factor contributing to the estrogenic activity of coumestrol. Opening of the furan ring leads to loss of activity. Bradbury and White[22] observed that 7,4'-dimethoxy--3-phenylcoumarin closely related to coumestrol was devoid of estrogenic activity.

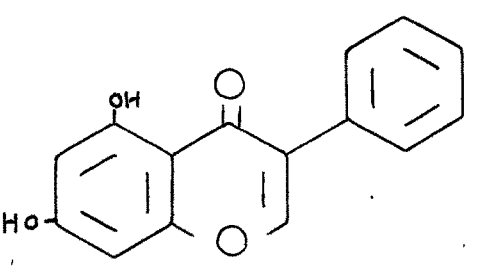
In the discussion section of a review article on estrogens by Biggers, Whalley[23], has suggested that the estrogenic activity of coumestrol couldbe attributed to its stilbene-like structure analogus to that of diethylstilbestrol (3). Coumestrol has a close structural relationship to stilbestrol as well to the natural estrogen estradiol (4). The ether bridge in coumestrol stabilizes the double bond in the 3-, 4-position to maintain stilbene-like structure. When this ring is opened, this double bond is free to resonate and keto-enol tautomerism exists[24] at the 4-position. As suggested by Whalley, this might explain why most of the 4-hydroxy-3-phenylcoumarin exhibit no estrogenic activity.



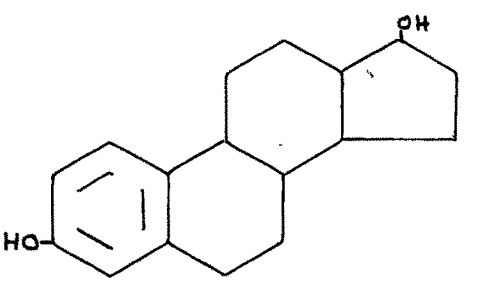

(2) Coumestrol.




(3) Diethylstilbestrol.



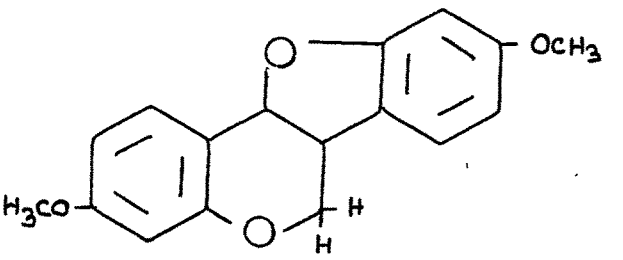

(5) Genistein.




(4) Estradiol.

Structural relationship of Genistein, Coumestrol, Estradiol and Diethylstilbestrol.

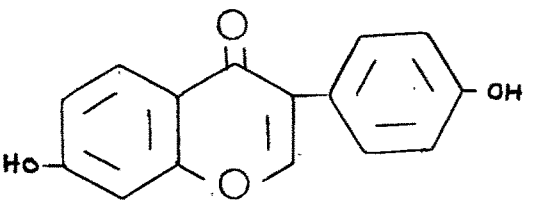
Additional evidence for the importance of stilbene-like structure of coumestrol is shown by the complete inactivity of homo-pterocarpin (6).




(6)

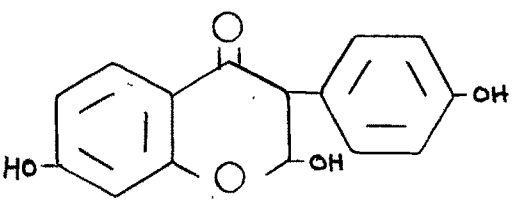
Bradbury[25] observed the striking similarity between the naturally occuring estrogenic isoflavone, one of which is genistein and the 3-phenyl-4-hydroxycoumarin. He pointed out that this close relationship is further emphasized by considering the addition of water across the double bond of an isoflavone to give 2-hydroxy isoflavne (8), followed by enolization to 2,4-dihydroxy-isoflav-3-en (fig. 1) (9).

Bate-Smith, quoted by Biggers[23], suggests that coumestrol may be derived in the plant by rearrangement of the isoflavonol corresponding to daidzein (7) with ring closure to the 6'-position (fig. 2). The fact that coumestrol is more that 30 times as active as the closely related estrogenic isoflavones[26], is probably due also to the fact that the oxygen atom at position 4 of the isoflavone is primarily ketonic, which results in a single bond in the 3,4-position.



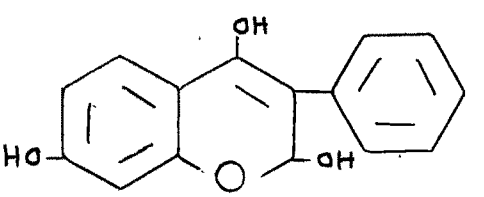

(7) Daidzein

$+H_2O$ ↓ ↑ $-H_2O$




(8) 2- Hydroxy Isoflavone

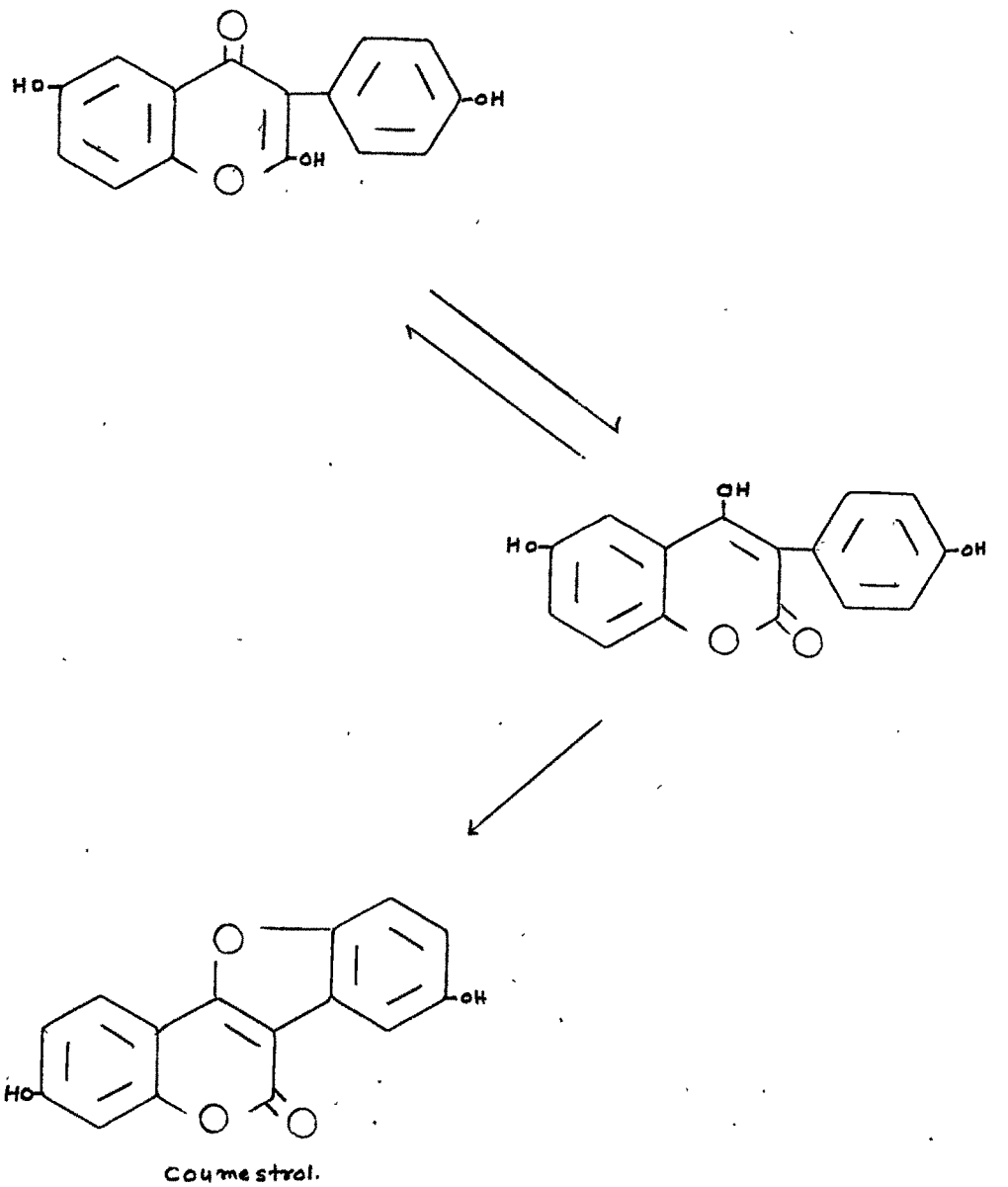
↓ ↑




2,4 - dihydroxy -isoflav-3-en

(9)

Suggested possibility of interconversion of isoflavones and isoflav-3-ens (Bradbury) (fig. 1).




Isoflavanol corresponding to Daidzein.

Suggested possibility of rearrangement of isoflavanol to coumestrol (Bate-Smith) (fig. 2).

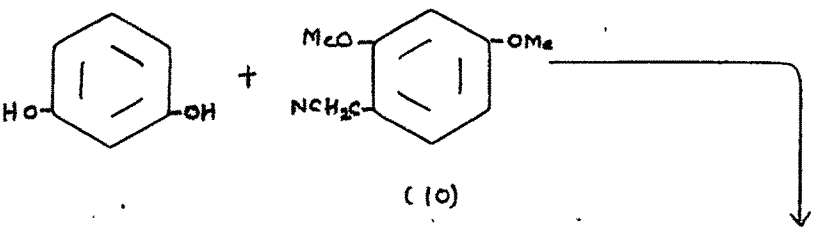
Just as the furan structure appears to be important for maintenance of the estrogenicity of coumestrol, so also does the α-pyrone ring structure. Opening of the ring with potassium hydroxide result in the formation of potassium salt of corresponding O-hydroxy-cinnamic acid, related to coumestrol. This compound is about equal active to coumestrol itself due to the ready conversion to coumestrol by the acidity of the stomach of animal.

The structure[9,27,28] of coumestan derivatives are established by fusion, stepwise degradation, synthesis, ultra-violet spectra and nuclear magnetic resonance spectra.

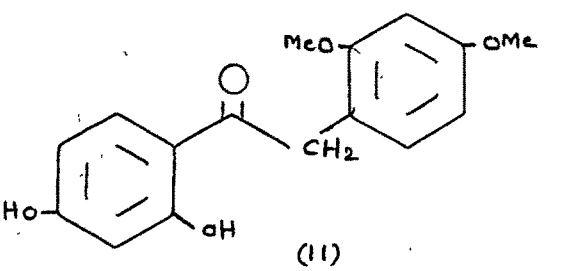
The method of synthesis of benzofuro (3,2-c) benzo-pyrans are reviewed here.

Emerson and Bickoff[29] condensed 2,4-dimethoxy phenyl acetonitrile (10) with resorcinol and obtained α-(2,4-dimethoxyphenyl-2,4-dihydroxy acetophenone (11), which on treatment with methyl chloroformate yields 3-(2,4-dimethoxy-phenyl)-4,7-dihydroxycoumarin (12). It was then cyclised by heating with aniline hydrochloride to coumestrol (2) in overall yield of about 17 %.

Govindachari et al.[30,31] have synthesised tri-o-methyl wedelolactone, Asaryladehyde, obtained in nearly quantitative yield, from 1,2,4-trimethoxy benzene by treatment with dimethyl formamide, was converted into 2,4,5-trimethoxy benzyl cyanide, through 2,4,5-trimethoxy phenyl pyrulic acid.

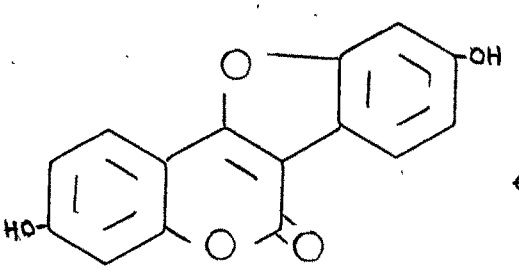



(10)



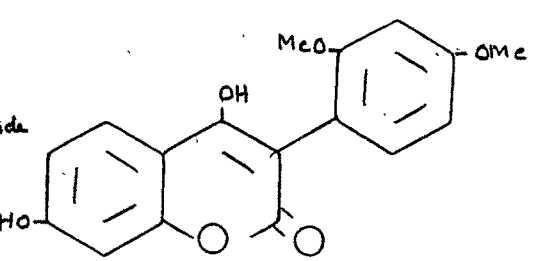

(11)

Methyl chloroformate.



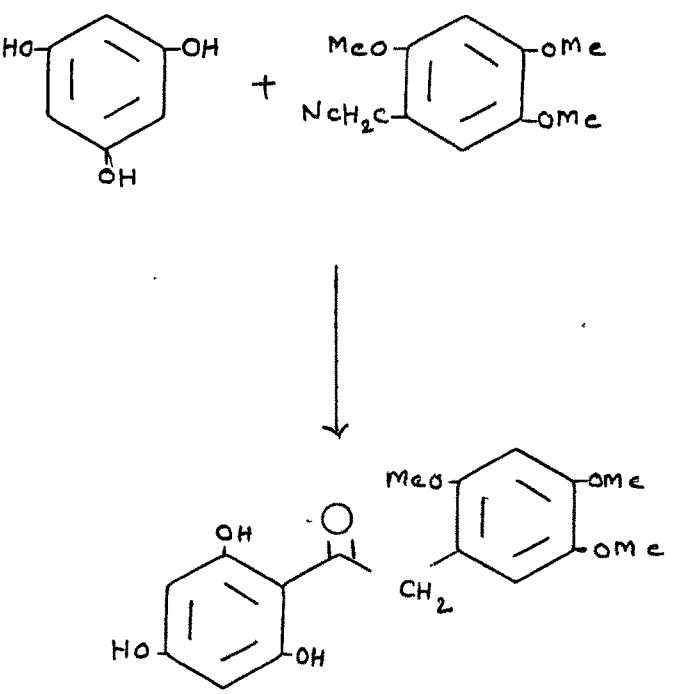

(1)

Anilina hydrochloride

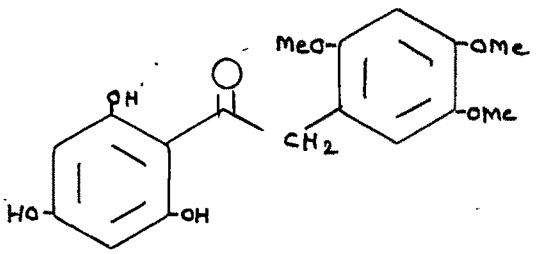



(12)

The deoxybenzoid (13) obtained by Hoesch reaction of this cyanide with phloroglucinol was converted by selective methylation into the dimethyl ether (14) and then by ethyl carbonate and sodium metal into the 4-hydroxycoumarin (15), which when heated with aniline hydrochloride was converted into the coumarónocoumarin, tri-o-methyl wedelolactone (16). Since the 7-methoxy group in a benzopyrone is the least easily attacked by acids, controlled treatment of the trimethyl ether with hydrogen iodide produces wedelolactone (17) identical with the natural product[32]. In this method sodium and diethyl carbonate was used for the preparation of 4-hydroxycoumarin instead of methyl chloroformate.

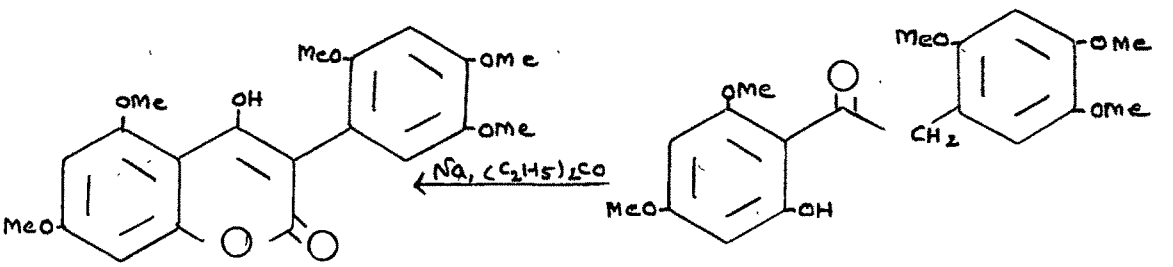



(13)




(13)

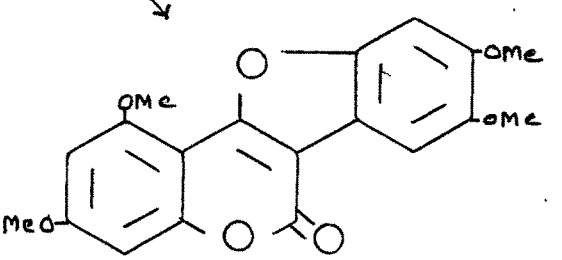
$(CH_3)_2SO_4$



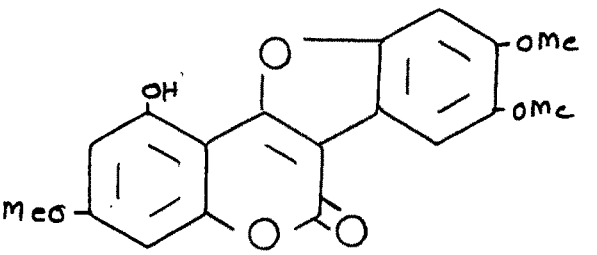

(15)

(14)

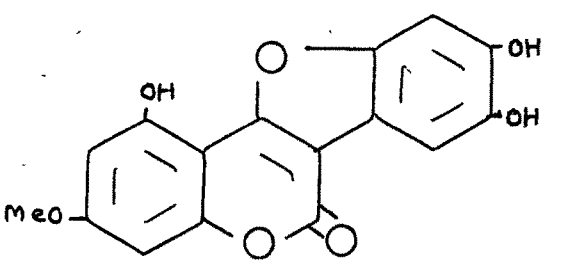
$C_6H_5NH_2 \cdot HCl$




(16)

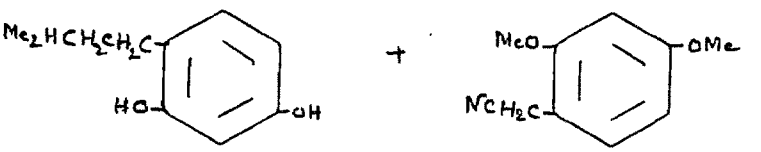



(16)

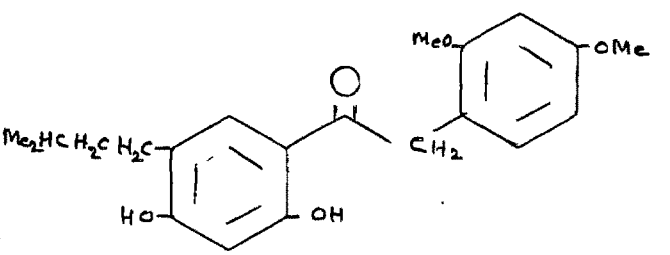



(17)

As psoralidin is labile to acids, it has not been synthesised but dihydropsoralidine (18) was prepared by standard methods[20,33,34]. Treatment of 2,4-dihydroxy-5-isopentyl-2,4-dimethoxy-benzyl ketone (19), obtained by Hoesch reaction of 2,4-dimethoxy benzyl cyanide and 4-isopentyl resorcinol with ethyl chloroformate, followed by treatment with alkali and then with acid gave 4,7-dihydroxy--6-isopentyl-3-(2',4'-dimethoxy phenyl) coumarin (20). Demethylation of the latter compound with aniline hydrochloride resulted in the formation of dihydropsoralidin (18).

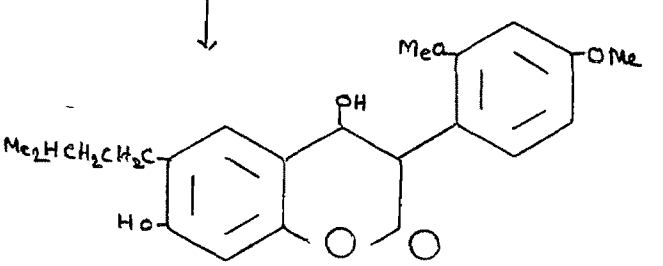


Hoesch reaction

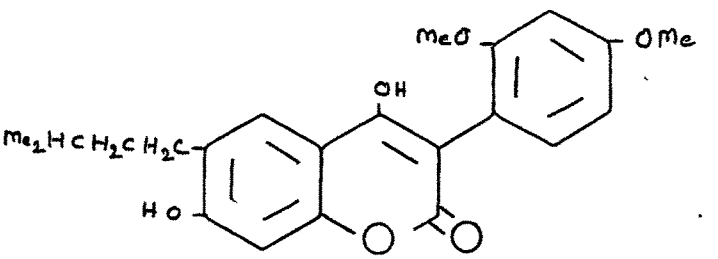


(19)

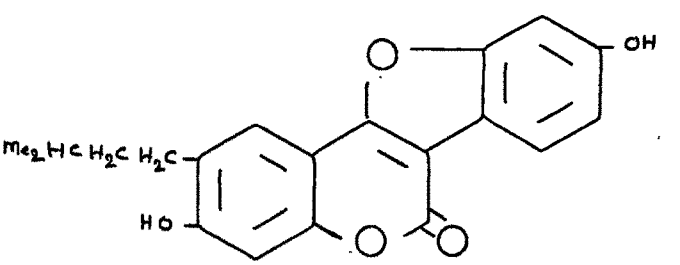
Ethyl chloroformate.



(20)

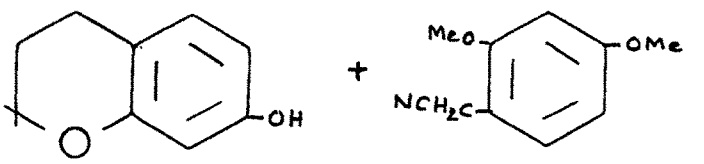



(20)

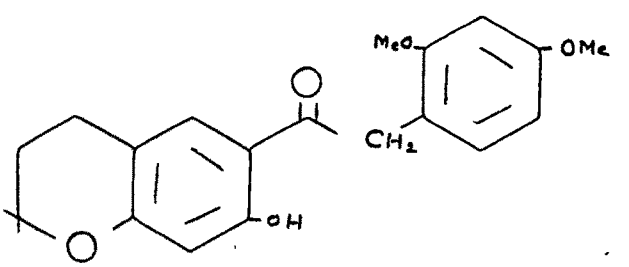



(18)

Isopsoralidin (21), isomeric hydroxy chroman is an acid catalysed rearranged product of psoralidine, has been synthesised by D. Nasipuri and G. Pyne[20,33]. Hoesch condensation of 2,4-dimethoxy benzyl cyanide with 2,2-dimethyl-7-hydroxy chroman (22) furnished 2,4-dimethoxy benzyl -7-hydroxy-2,2-dimethylchroman-6-yl-ketone (23), which was converted into the 4-hydroxycoumarin derivative (24), by ethyl chloroformate and thence into isopsoralidine (21) by heating it with aniline hydrochloride.

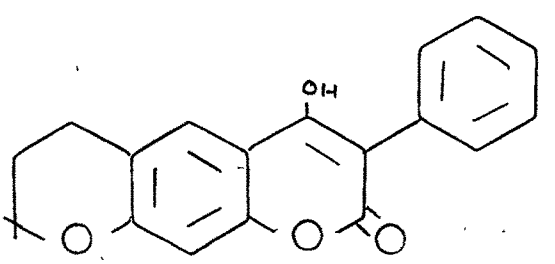



(22)

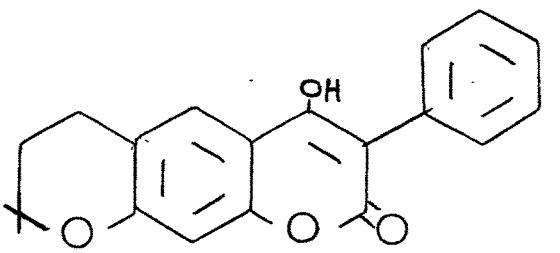



(23)

Ethyl chloroformate.

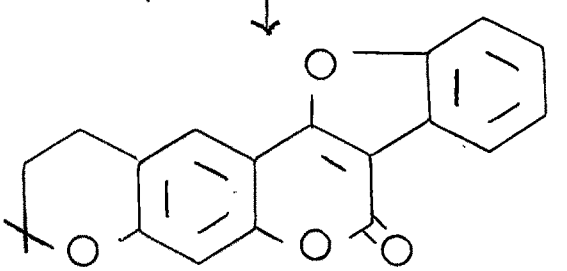



(24)



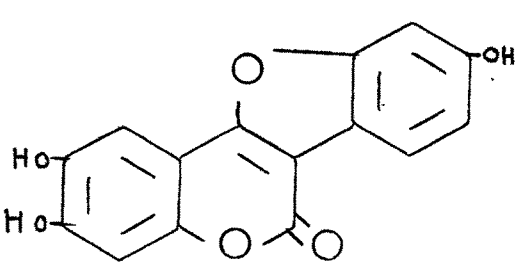
(24)

Aniline hydrochloride

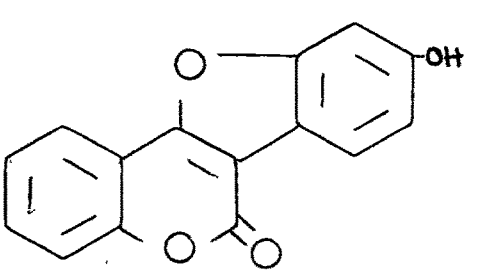


(25)

V.K.Karla and his co-workers[34] synthesised lucernol and sativol dimethyl ether using this method.



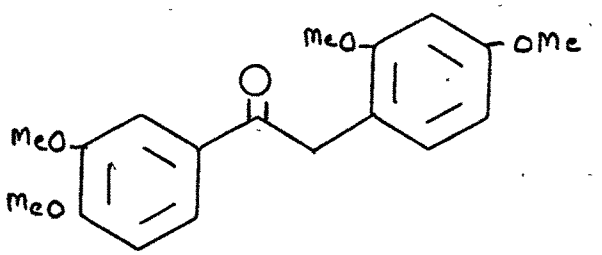
Lucernol



sativol

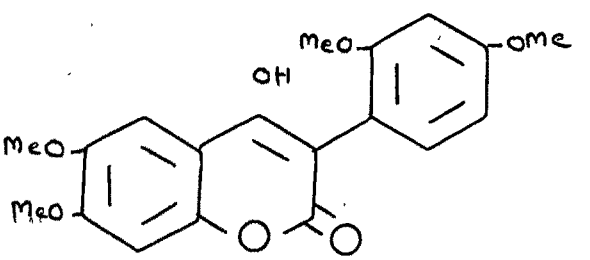
2-Hydroxy-4,5-dimethoxy phenyl-2,4-dimethoxy benzyl ketone (25), a key intermediate in the synthesis of lucernol was prepared by following route. Friedle-Crafts reaction of 2,4-dimethoxy phenyl acetyl chloride with 1,2,4-trimethoxy benzene gave a mixture of 2-methoxy and hydroxy ketones. The partial demethylation was completed by refluxing with aluminium chloride in methyl cyanide (1/2 hour) yielded the required 2-hydroxy ketone (25). Cyclisation of (25) with ethyl chloroformate gave 6,7,2',4'-tetramethoxy-3-phenyl-4-hydroxycoumarin (26). Demethylative ring closure with hydrogen iodide at (bath temperature 170°) for 2 hours in carbon dioxide atmosphere yielded lucernol (27). Its purity was established by TLC and Paper Chromatography. It was identical with an authentic sample of natural lucernol in TLC, Paper Chromatography, Spectra and mixed melting point.

2-Hydroxy-3,4-dimethoxy-phenyl-2,4-dimethoxy benzyl ketone (28) was cyclised with ethyl chloroformate to 7,8,2',4'-tetramethoxy-3-phenyl-4-hydroxycoumarin (29). Demethylative ring closure with hydrogen iodide (bath temperature 100°) for five minutes yielded a mixture which on methylation with dimethyl sulphate and potassium carbonate in acetone gave sativol dimethyl ether (30) identical in chromatography behaviour, spectra and mixed melting point with the dimethyl ether of natural sativol.



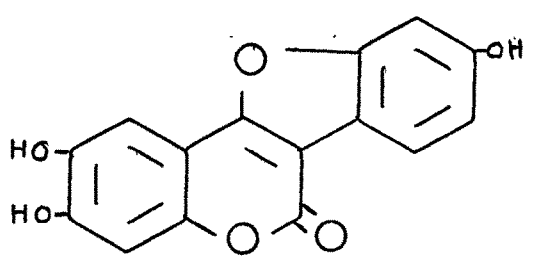

(25)

Ethyl chloroformate

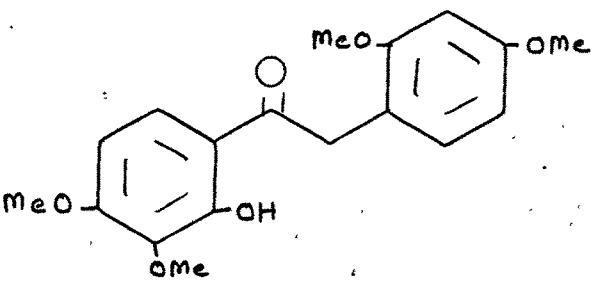



(26).

HI in $CO_2$

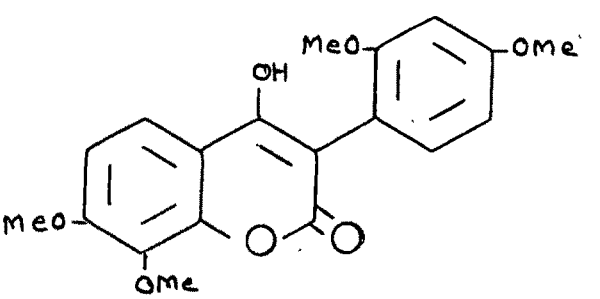



(27)



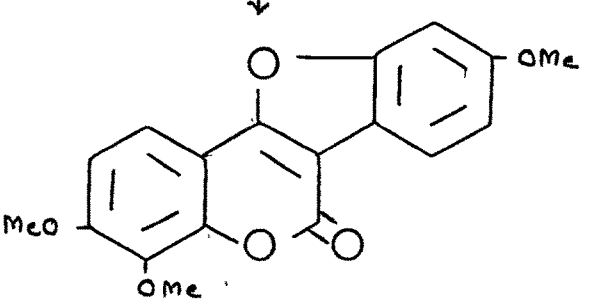

(28)

Ethyl chloroformate.



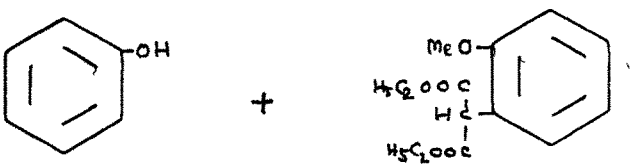

(29)

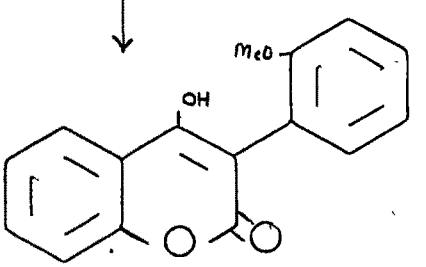
$HI$, $(CH_3)_2SO_4$.
$K_2CO_3$, Acetone



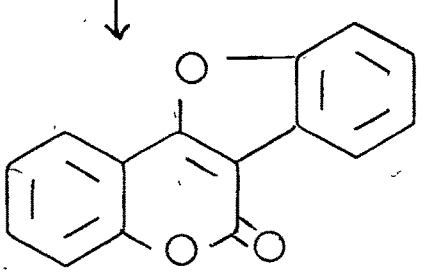

(30)

(2) Coumestan was synthesised by Mentzer et al.[35] Thermal condensation of equimolar amounts of o-methoxyphenyl malonate with phenol gave 3-(2-methoxyphenyl)-4-hydroxycoumarin (31), which on treatment with pyridine hydrochloride produced coumestan (1)



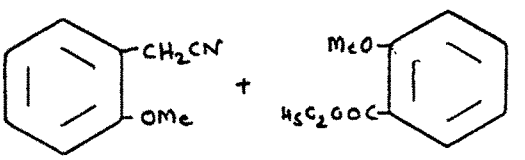




(31)

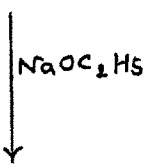


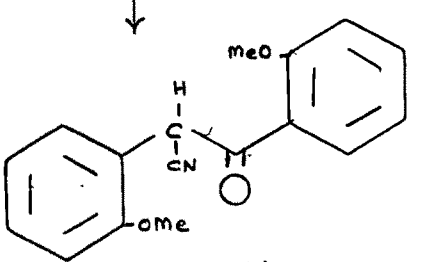

(1)

(3) Coumestan was also synthesised by Chatterjea and Roy[36]. They condensed o-methoxy phenyl acetonitrile (32) with ethyl o-methoxy benzoate (33) in the presence of sodium ethoxide and obtained an intermediate ketonitrile (34) which on treatment with hydro bromic acid[37] gave coumestan (1).

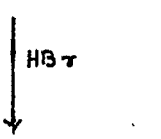


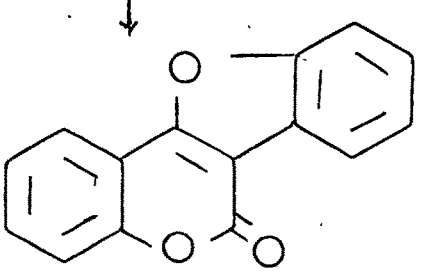

(32) (33)




(34)



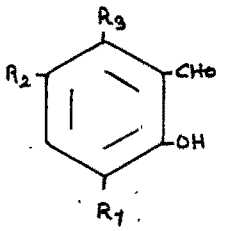




(1)

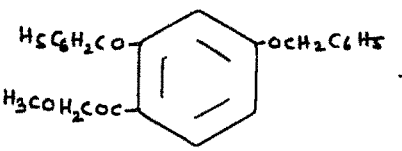
(4) Coumestrol and series of related isomers of coumestrol were synthesised by hydrogen peroxide oxidation of appropriately substituted 2'-hydroxy-3-methoxy flavylium salts[38,39]. An appropriately substituted o-hydroxy benzaldehyde (35) was condensed in an etheral hydrogen chloride solution with ω-methoxy-2,4-dibenzyloxy acetophenone (36). The salt is debenzylated with hydrochloric acid to give the desired flavylium salt (37). The salt is oxidised with hydrogen peroxide in aqueous methanol to give the 3-carbomethoxy benzofuran (38), which is then rapidly hydrolysed and lactonises on acidification to give coumestan derivatives (39). The orientation pattern of the ring (D) is governed by the aldehyde (35). An aldehyde (35) substituted at $R_1$ $R_1(R_2=R_3=H)$ will produce substitution in the 13-position of the (D) ring (39). Similarly $R_2(R_1=R_3=H)$ substituted aldehydes produces the 11-series and $R_3(R_1=R_2=H)$ the 10-series.

Trifoliol was synthesised by this method. 5-Benzoyloxy-7-hydroxy-3-methoxy-2',4'-dibenzyloxy flavylium chloride (40), on peroxide oxidation gave the intermediate (41) which was methylated to (42) and then debenzylated to yield 7-benzyloxy-3-hydroxy-9-methoxycoumestan (43). Alkaline hydrolysis of the latter compound furnished 3,7-dihydroxy-9-methoxycoumestan (trifoliol) (44).

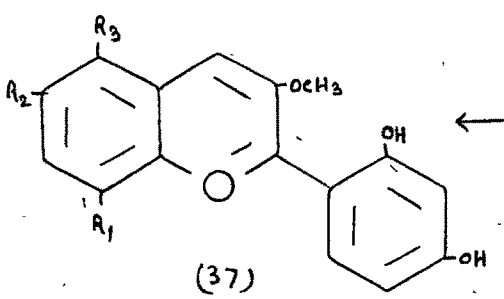
Trifoliol is the first reported natural product containing a substituted phloroglucinol-like structure in ring (D). This is of particular bio-synthetic interest because it was thought that only the ring (A) of flavonoids arises



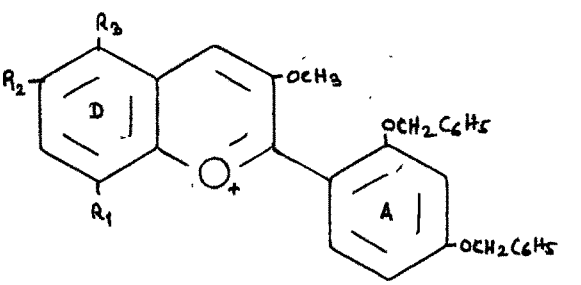

(35)



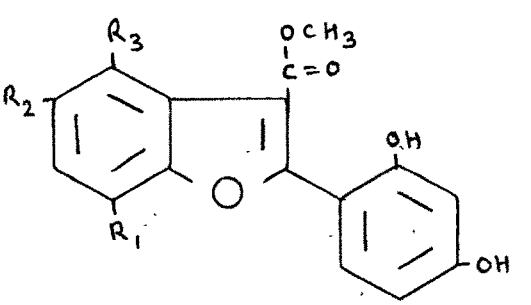

(36)



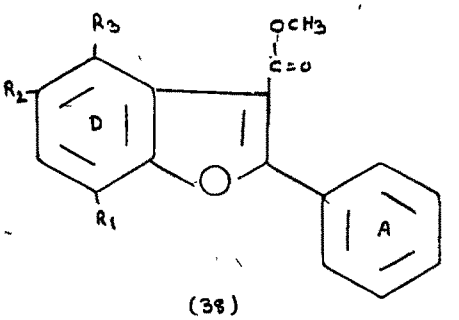

(37)




$H_2O_2$ in methanol.

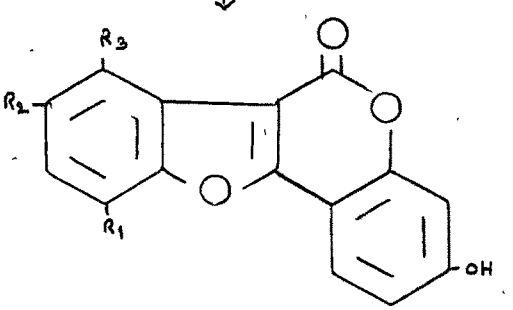



(38)



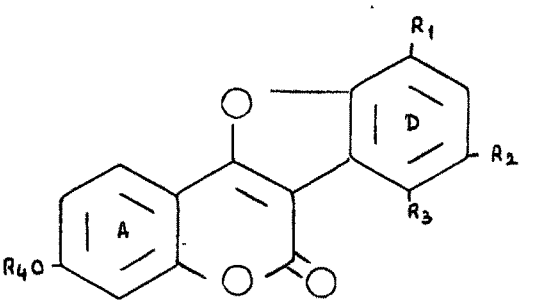

(38)

Acidification



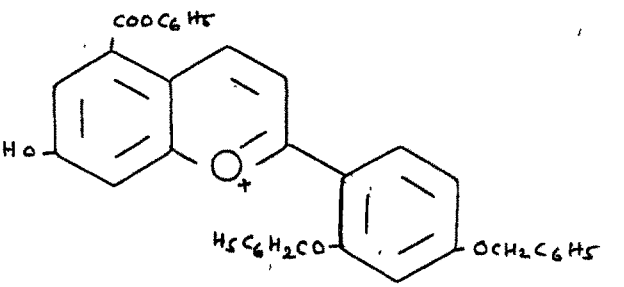

(39)

OR

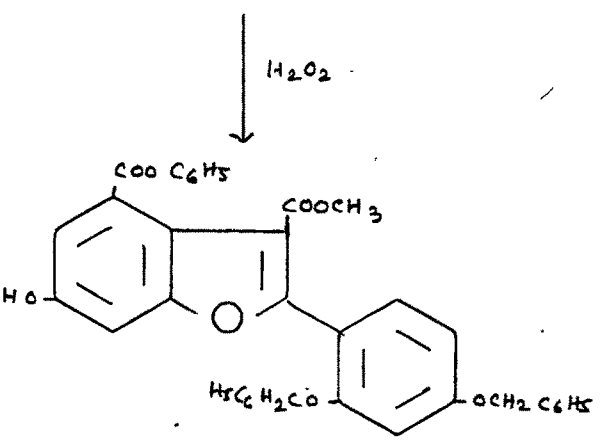



(39)

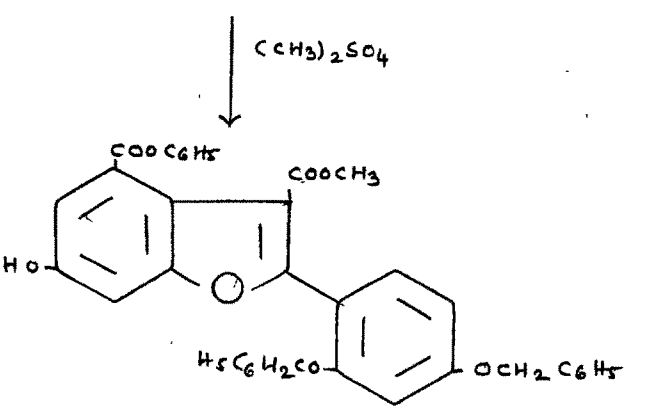
from phloroglucinol[40]. Trifoliol has no oestrogenic activity, in contrast to the parent phenol (45), which is as active as coumestrol[41].



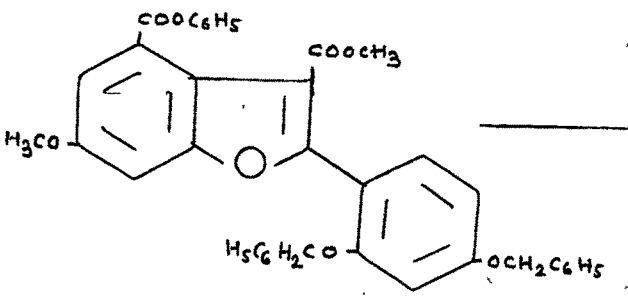
(40)



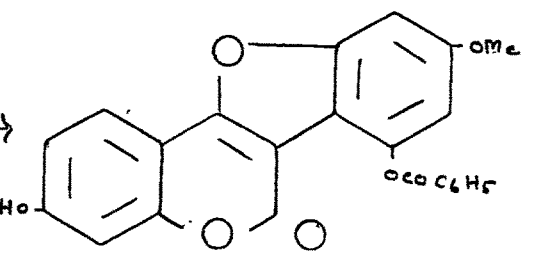
(41)



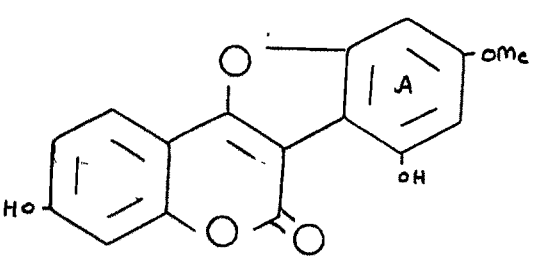
(42)


COOC6H5
COOCH3
H3CO
H5C6H2CO
OCH2C6H5

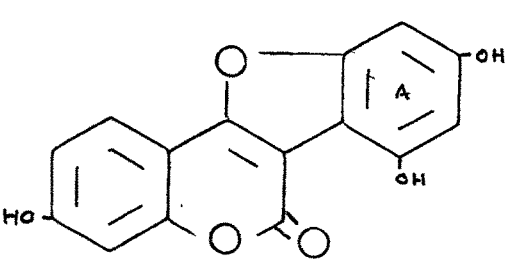
(42)


OMe
HO
OCO C6H5

(43)


OMe
A
OH
HO

(44)


OH
A
OH
HO

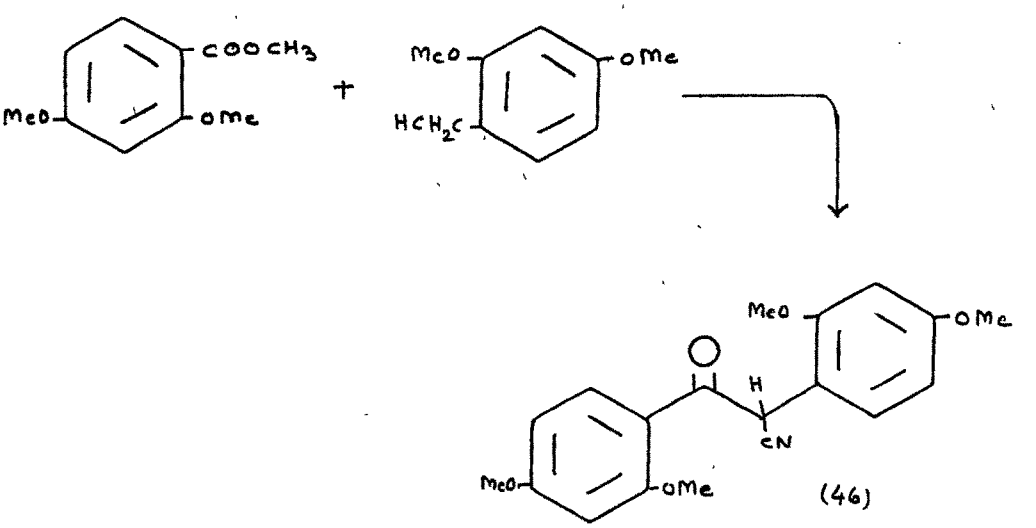
(45)

L. Jurd[42] has synthesised medicagol recently by carrying out hydrogen peroxide oxidation of 3-methoxy-6,7-methylene-dioxy-2',4'-dihydroxy flavylium chloride.

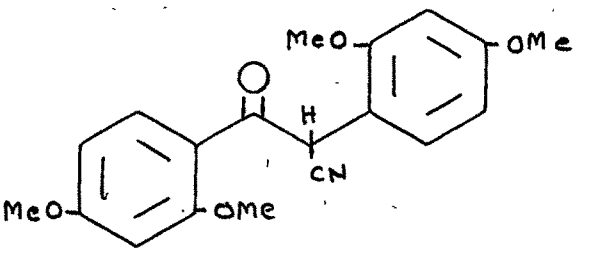
L. L. Simonova and A. A. Shamshurin[43] synthesised 7,11-dihydroxycoumestan by peroxide oxidation of 2',4',6'-trihydroxy-3-methoxy flavylium chloride.

Spencer, Knuckles and Bickoff[44] synthesised 7-hydroxy-11,12-dimethoxycoumestan by hydrogen peroxide oxidation of 6,7,2',4'-tetrahydroxy flavylium chloride and selective methylation of 7,11,12-trihydroxycoumestan.

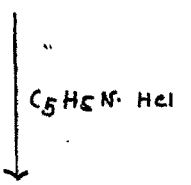
(5) Yoshiyuki Kawase[45] synthesised coumestrol by the following method. The ketonitrile (46) obtained by condensation of methyl-2,4-dimethoxy benzoate and 2,4-dimethoxy benzyl cianide in the presence of sodium hydride, was treated with pyridine hydrochloride to give coumestrol.

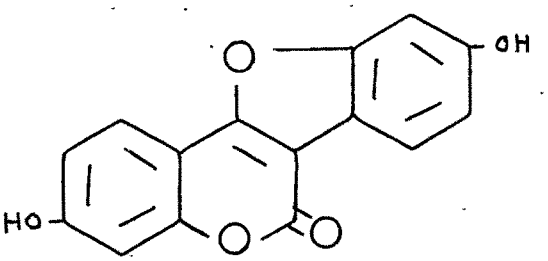



(46)

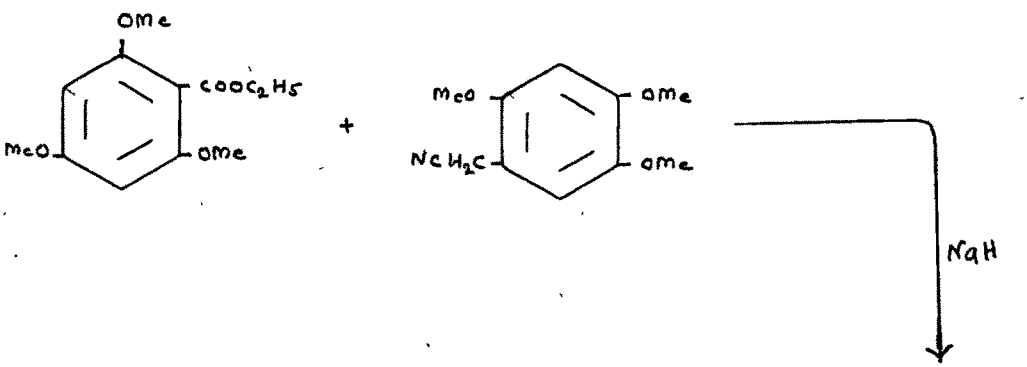


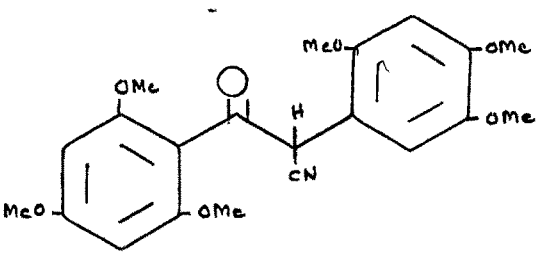

(46)



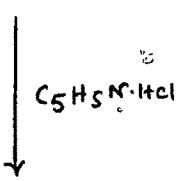



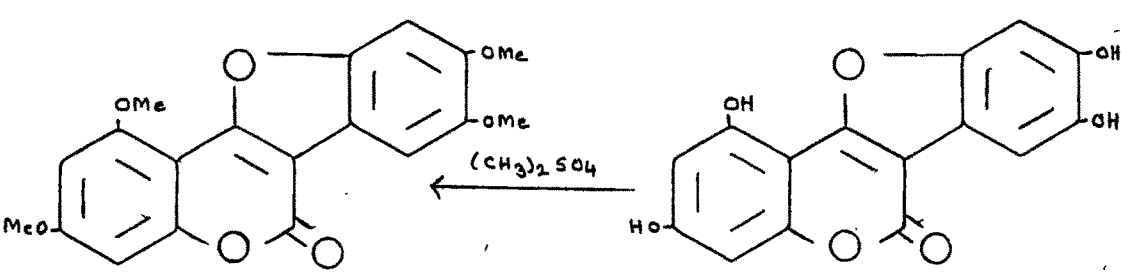

Chatterjea and Prasad[46] have recently synthesised tri-O-methyl-wedelolactone by the method of Yoshiyuki and Kawase[45]. The ketonitrile (47) obtained by condensation of 2,4,5-trimethoxy benzyl cyanide and ethyl-2,4,6-trimethoxy benzoate in the presence of sodium hydride, was treated with pyridine hydrochloride to yield (48), which was readily methylated tri-O-methyl wedelolactone (16).


OMe
COOC2H5
MeO
OMe
+
MeO
OMe
NCH2C
OMe
NaH


MeO
OMe
OMe
H
CN
MeO
OMe

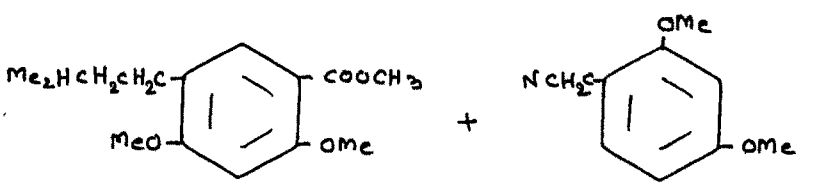
(47)


C5H5N·HCl

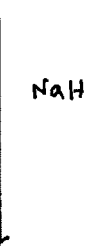

OMe
OMe
OMe
MeO
(CH3)2SO4
OH
OH
OH
HO

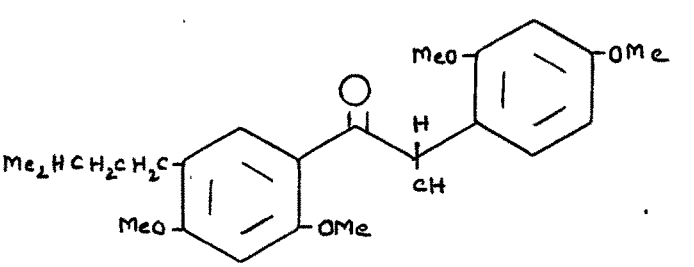
(16) (48)

Chatterjea, Banerji and Prasad[47] have synthesised dihydropsoralidin by using the method of Yoshiyuki Kawase. Treatment of the ketonitrile, α-(2,4-dimethoxy-5-isopentyl-benzoyl)-2,4-dimethoxy benzyl cyanide (49), obtained by condensation of methyl-2,4-dimethoxy-5-isopentyl benzoate (50) and 2,4-dimethoxy benzyl cyanide, in the presence of pyridine hydrochloride, led to the formation of dihydro-psoralidine (18).

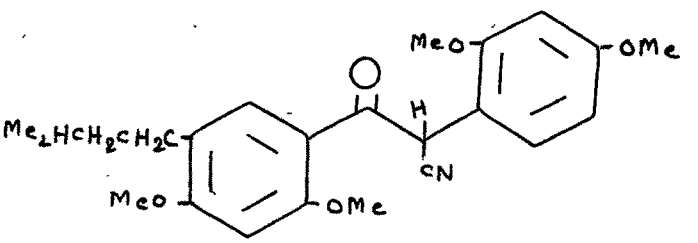



(50)

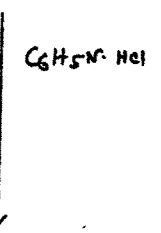


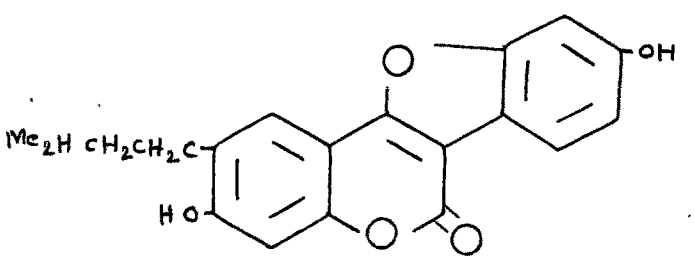




(49)



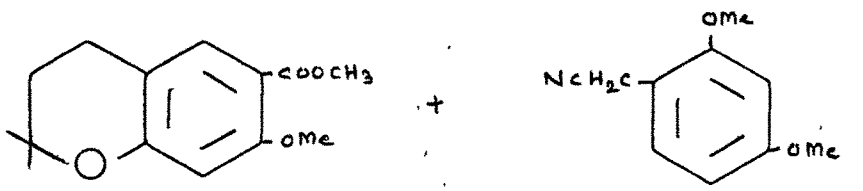

(49)



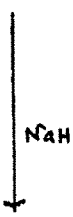



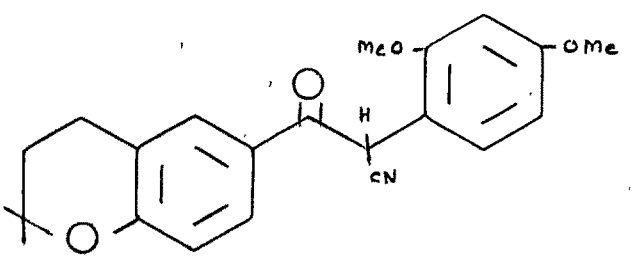

(18)

Chatterjea, Banerji and Prasad[47] synthesisdd iso-psoralidin by using this method. They have condensed methyl-2,3-dimethyl-7-methoxy chroman benzoate (51) with 2,4-di-methoxy benzyl cyanide in the presence of sodium hydride to obtain ketonitrile (52) gave treatment of it with pyridine hydrochloride gave isopsoralidin.

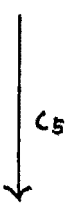


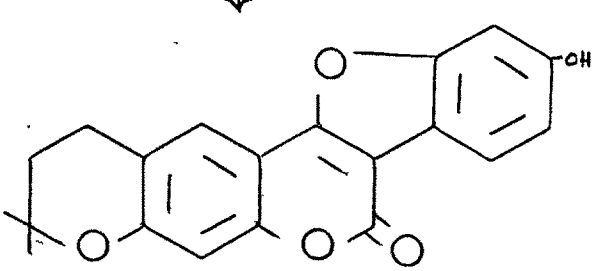

(51)



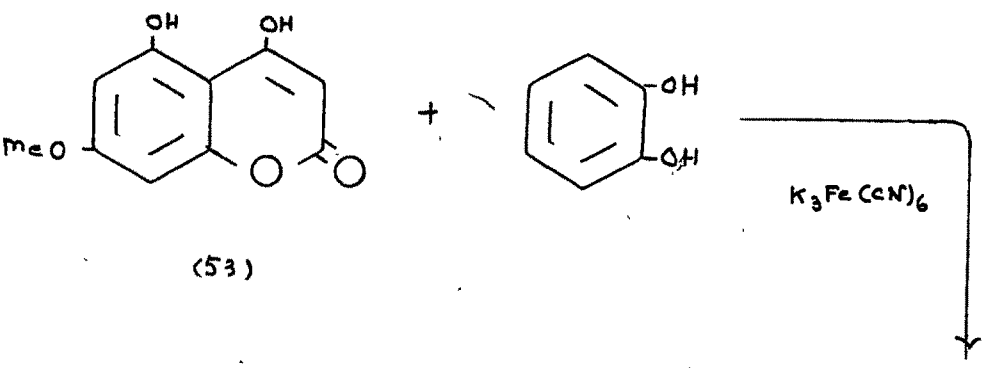

(52)



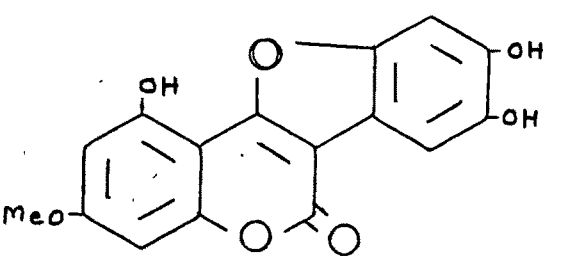




(21)

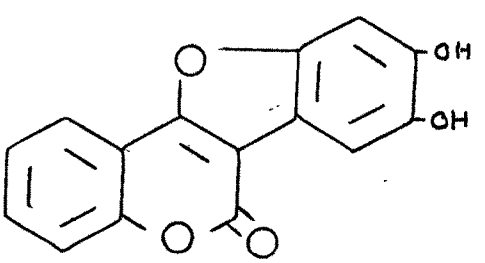
(6) Wanzlick and co-workers[48] prepared wedelolactone (17) by dehydrogenative coupling of catachol with 4,5-dihydroxy-7-methoxycoumarin (53) obtained by partial methylatton of4,5,7-trihydroxycoumarin with methyl sulphate and sodium carbonate and potassium ferricyanide. Similarly, the angular coumaronocoumarin (54) was obtained by dehydrogenation of catachol in the presence of 4-hydroxycoumarin and a mixture of sodium acetate and potassium iodate.




(53)

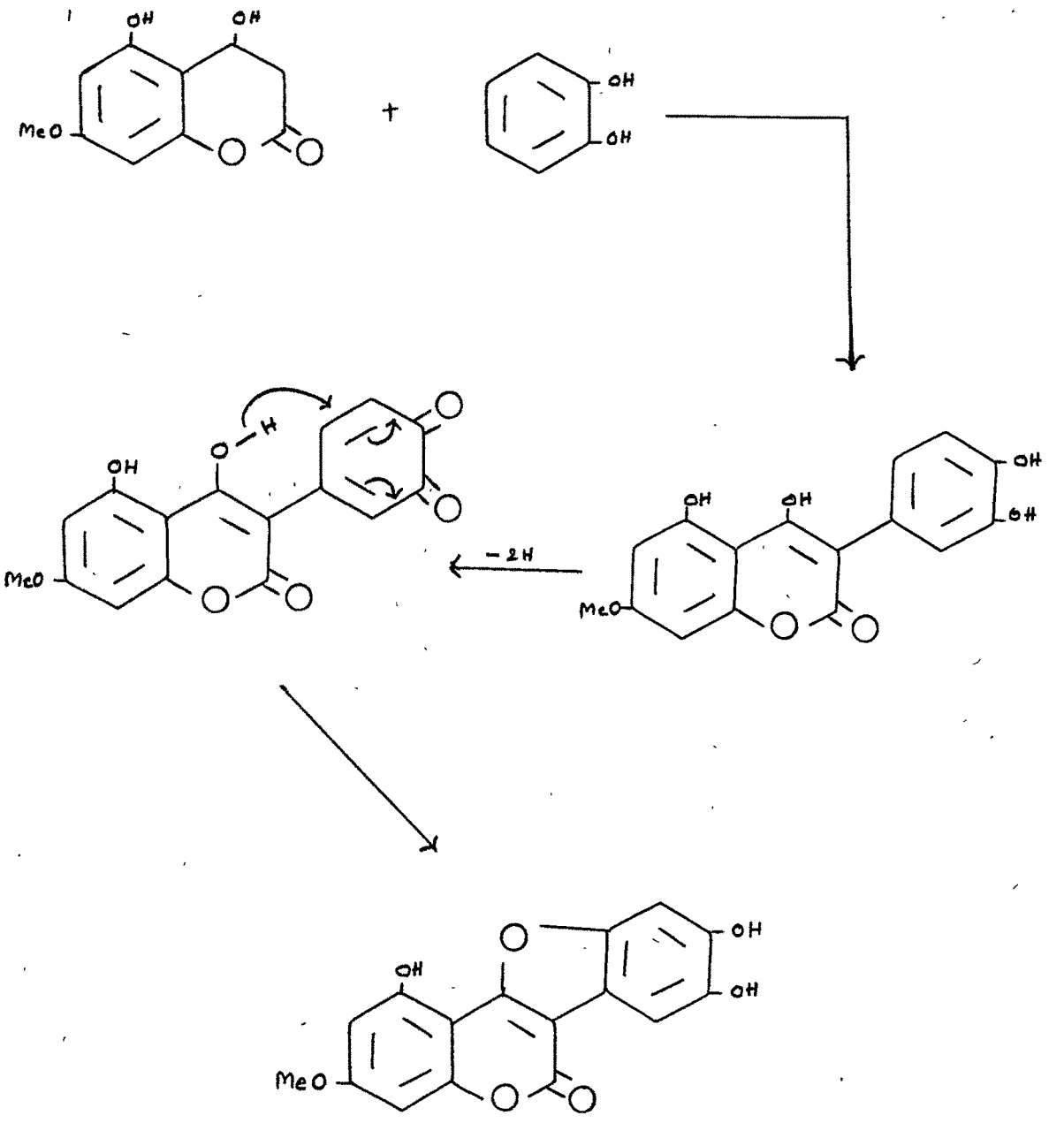



(17)

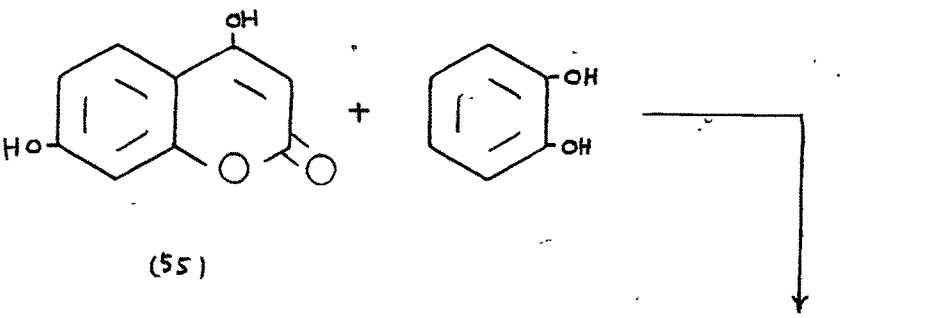



(54)

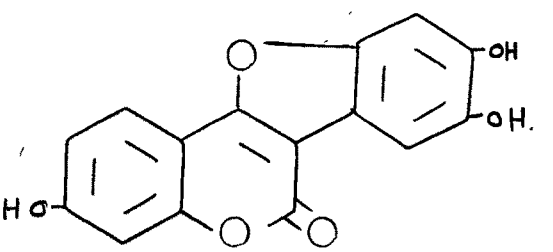
The mechanism given by the authors is as shown below :-



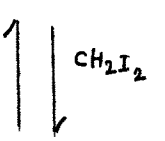
Medicagol was synthesised by using this method. 4,7-Dihydroxycoumarin (55) which was oxidatively coupled with catachol[48]. Methylation of (56) with diiodomethane gave (57).

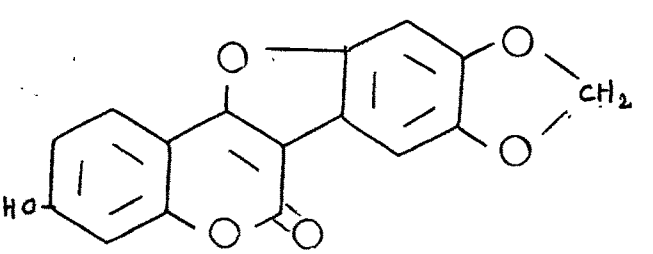



(55)




(56)



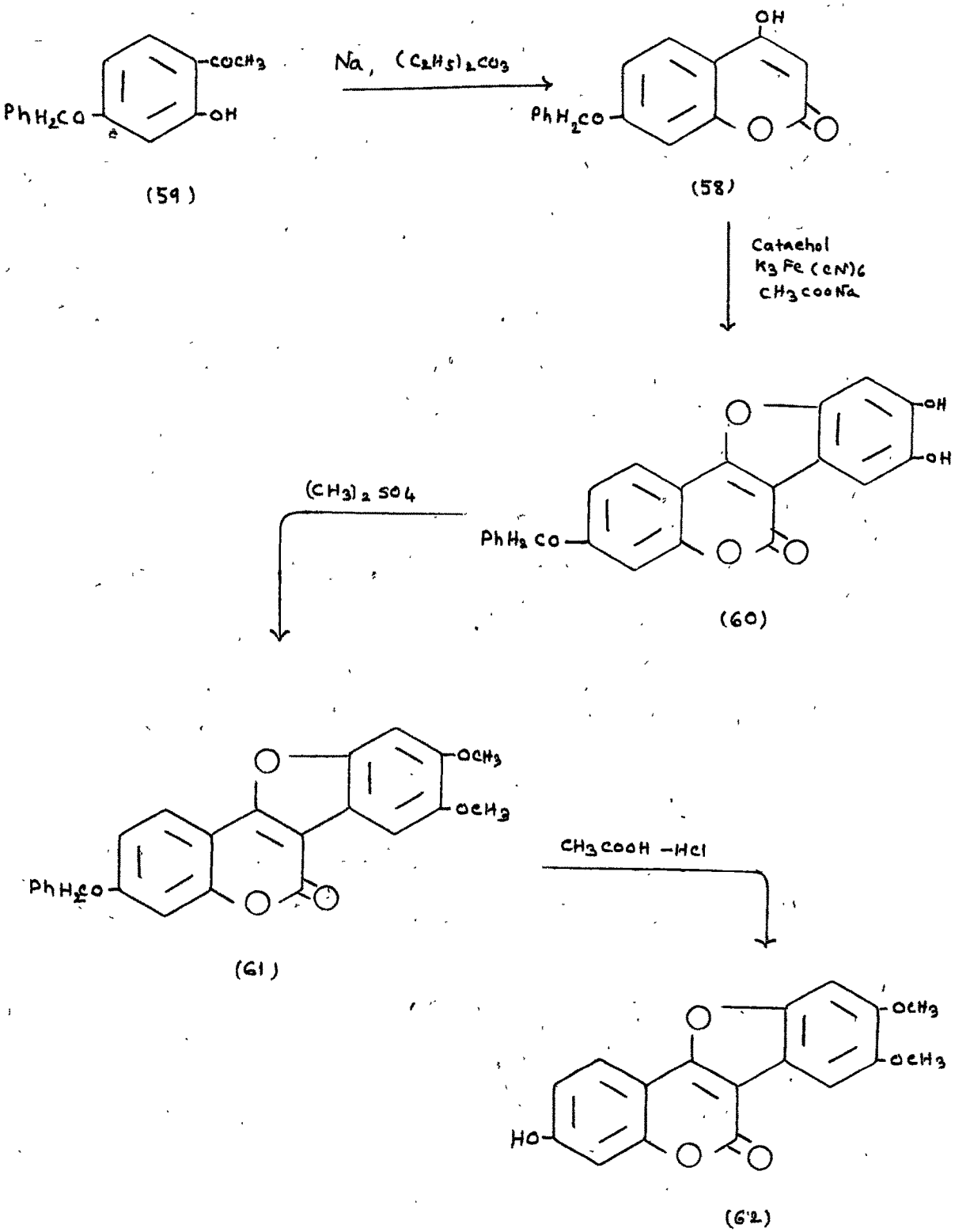



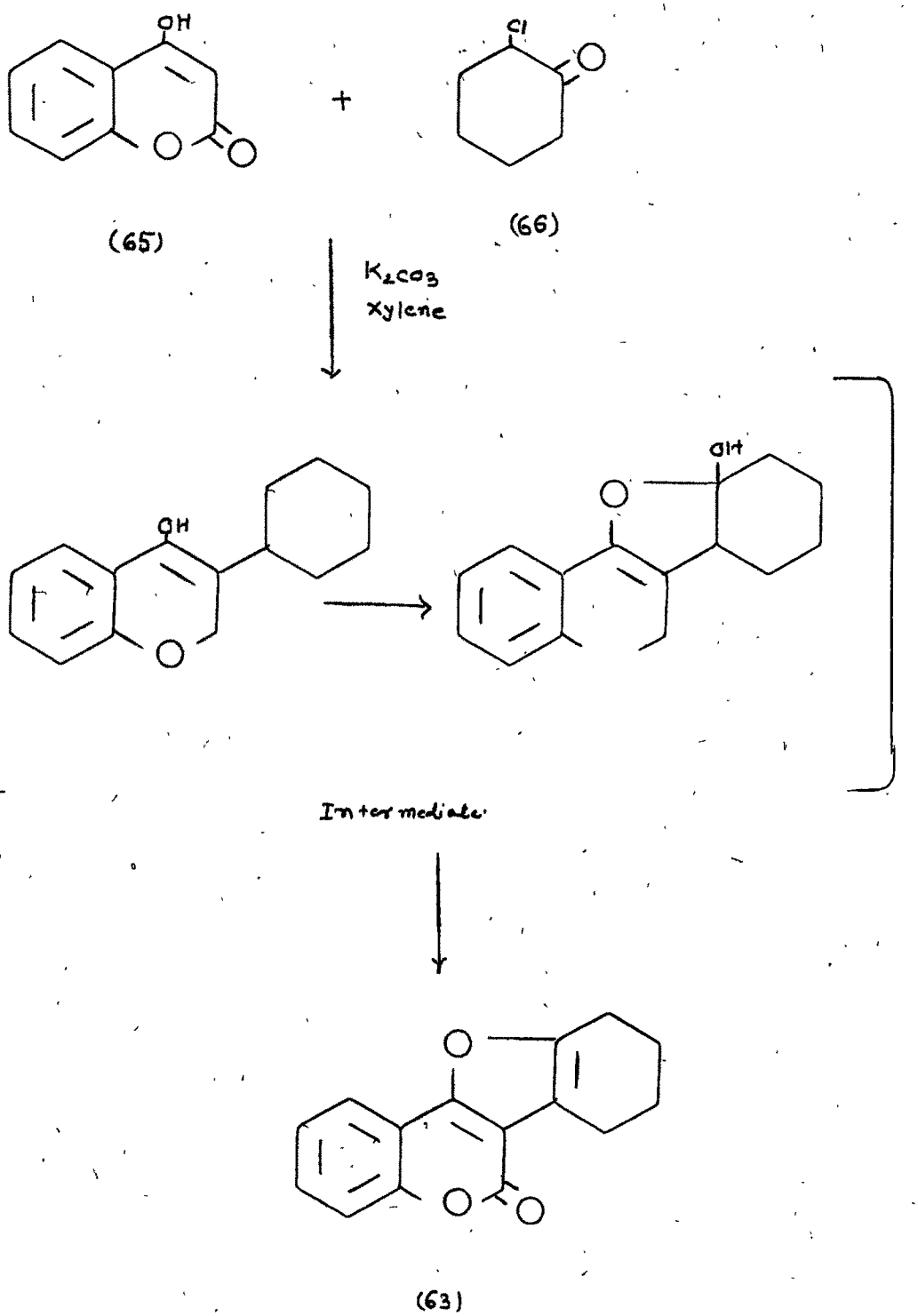

(57)

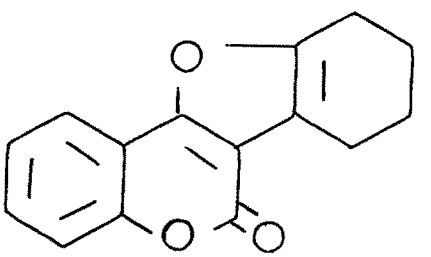
Subba Rao and co-workers[49] synthesised 7-hydroxy-11,12-dimethoxycoumestan by the method of Wanzlick. 7-Benzyloxy-4-hydroxycoumarin (58) was prepared by the condensation of 4-benzyloxy-2-hydroxy acetophenone (59) with sodium and ethyl carbonate adopting Boyd-Robertson method. Dehydrogenative condensation with catachol in the presence of potassium ferricyanide and sodium acetate gave 7-benzyloxy-11,12-dihydroxycoumestan (60), which on methylation afforded dimethyl ether (61), debenzylation with glacial acetic acid and hydrochloric acid (1 : 1) gave 7-hydroxy-11,12-dimethoxy-coumestan (62).

Triacetate of 7,11,12-trihydroxycoumestan was prepared by A.A.Shamshurin and L.L.Simonova[50]. It was prepared by treating catachol with 4,7-dihydroxycoumarin and potassium hypoiodate in the presence of sodium acetate in a water-acetone medium at a 20-40°. The resulting 11-hydroxycoumestrol is treated with acetic anhydrided in the presence of sodium acetate at the boiling point of the reaction mixture tri-a acetate of 7,11,12-trihydroxy coumestan (stimol-4100).

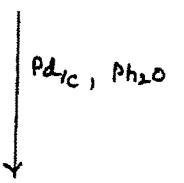
Subba Rao and co-workers[51] synthesised number of tetrahydrocoumestan (63) and coumestan derivatives (64) in 45-55 % yield by treating 4-hydroxycoumarin (65) with 2-chlorocyclohexanone (66) in boiling xylene using anhydrous potassium carbonate as a basic condensing agent.

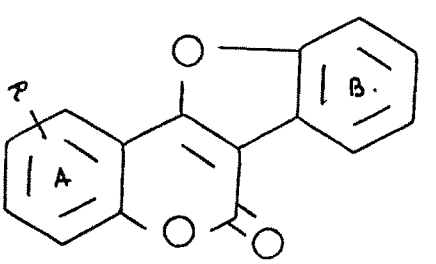

COCH3
PhH2CO
OH
Na, (C2H5)2CO3
OH
PhH2CO
(59)
(58)
Catechol
K3Fe(CN)6
CH3COONa
OH
OH
PhH2CO
(CH3)2SO4
(60)
OCH3
OCH3
PhH2CO
(61)
CH3COOH –HCl
OCH3
OCH3
HO
(62)


OH
Cl
(65)
(66)
$K_2CO_3$
Xylene
OH
OH
Intermediate
(63)



(G3)



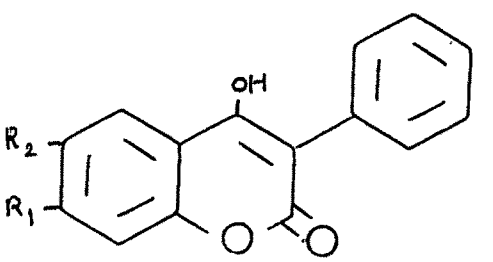




(G4)

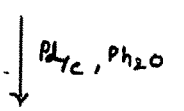
R=6-methyl, 7-methyl, 6-chloro.

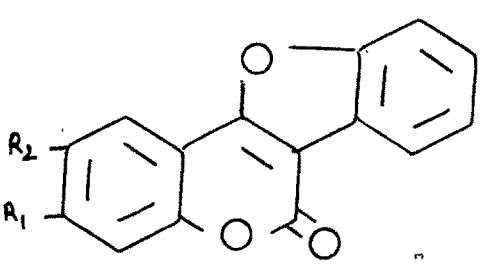
This method constitutes a new route for the synthesis of coumestan with different substitution in the ring A.

Thomas Kappe and Schmidt[52] synthesised coumestan derivatives starting with 4-hydroxy-3-phenylcoumarin derivatives. Cyclodehydrogenation of 4-hydroxy-3-phenyl-coumarin derivatives (67) in refluxing diphenyl ether containing 10 % palladised charcoal, while air is bubbled through the reaction mixture, gave the corresponding coumestan derivatives (68).




(67)(a-d)




(68)(a-d)

a, $R_1 = R_2 = H$

b, $R_1 = -CH_3$, $R_2 = H$.

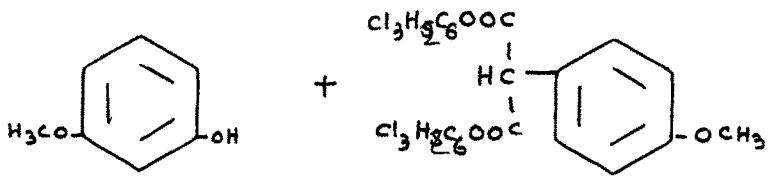
C, $R_1 = R_2 = -CH_3$

D, $R_1 = -OCH_3$, $R_2 = H$.

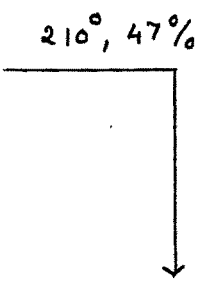
The coumestan (68) (a-d) can be easily separated from the starting material by their insolubility in dilute sodium hydroxide solution. They show a blue fluorescence on thin layer chromatography under ultra violet light. In the NMR spectra, the downfield shift of the proton at position $\delta$ 7 to $\delta$ 8.0-8.3 is characteristic for these compounds.

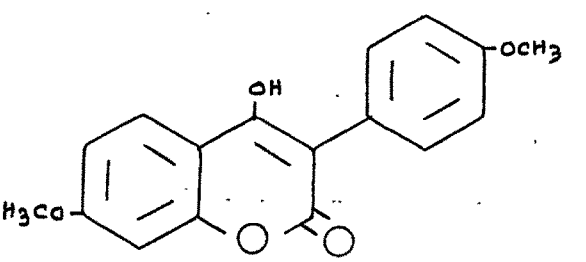
Thomas Kappe and Brandner[53] synthesised also coumestrol by using the above procedure. The thermal condensation of resorcinol monomethyl ether (69) with Di-2,4,6-trichloro phenyl-(4-methoxy phenyl) malenate (70) at 210° for 15 minutes gave to 4-hydroxy-3-(4'-methoxy-phenyl)-7-methoxycoumarin (71), which underwent cyclode-hydrogenation with palladised charcoal ( 10 %), to give 3,9-dimethoxycoumestan (72), which on demethylation with HBr-HOAC gave coumestrol.

Dholakia and Trivedi[54] synthesised following coumestan derivative by oxidative condensation of catachol with different 4-hydroxycoumarins followed by methylation. 2-Methyl-8,9-dimethoxy-6H-benzofuro (3,2-c) benzopyran (73 a), 2,8,9-trimethoxy-6-oxo-6H-benzofuro (3,2-c) benzopyran (73 b), 4-methyl-3,8,9-trimethoxy-6-oxo-6H-benzofuro (3,2-c) benzo-pyran (73 c), 1,8,9-trimethoxy-6-oxo-6H-benzofuran (3,2-c) benzopyran (73 d) and 3,4,8,9-tetramethoxy-6-oxo-6H-benzo-furo (3,2-c) benzopyran (73).

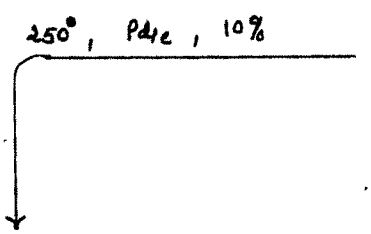


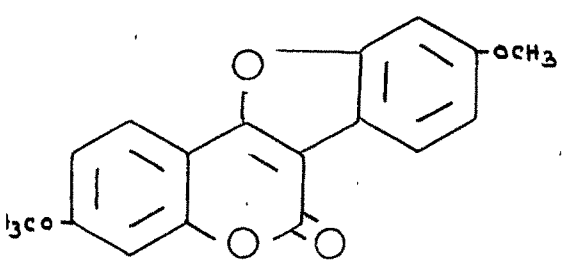
(69) (70)



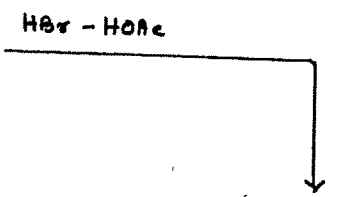



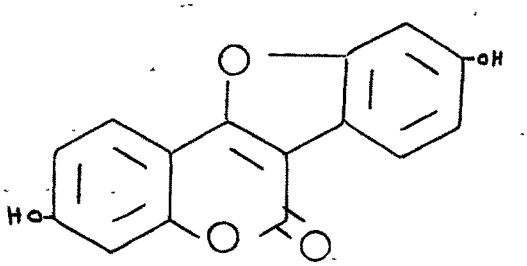
(71)

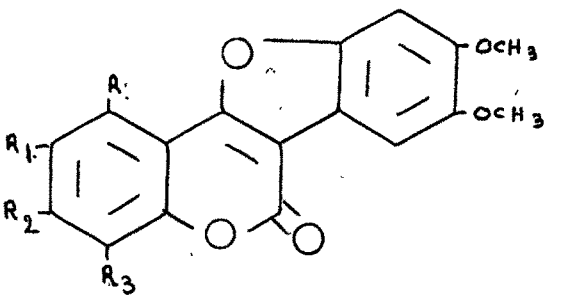


(72)






73 a, $R = R_2 = R_3 = H$; $R_1 = -CH_3$.

73 b, $R = R_2 = R_3 = H$; $R_1 = -OCH_3$.

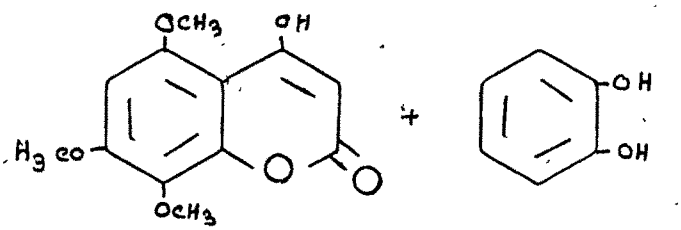
73 c, $R = R_1 = H$; $R_2 = -OCH_3$ ; $R_3 = -CH_3$.

73 d, $R = -OCH_3$; $R_1 = R_2 = R_3 = H$.

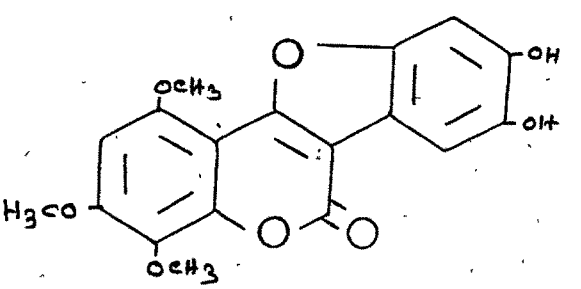
73 e, $R = R_1 = H$; $R_2 = R_3 = -OCH_3$.

Shaikh and Trivedi[55] synthesised 1,3,4,8,9-pentamethoxy-6-oxo-6H-benzofuro (3,2-c) benzopyran (74) by oxidative coupling of 5,7,8-trimethoxy-4-hydroxycoumarin with catachol in the presence of potassium iodate and sodium acetate followed by methylation with dimethyl sulphate.

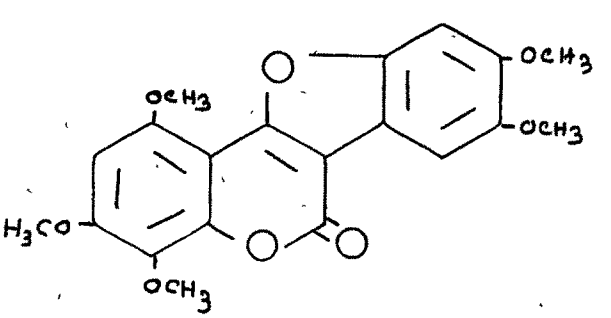
Coumaronofurocoumarins are the compounds in which a furan ring is fused to the coumarono-coumarin ring. This group is represented by the natural occurence of erosnin (75), isolated from the seeds of phacyrrhizus erosus (yam-beans).



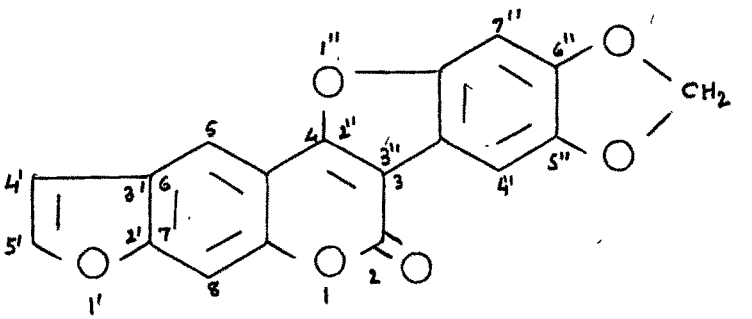
$KIO_3$, NaOAc



$(CH_3)_2SO_4$
$K_2CO_3$
Acetone



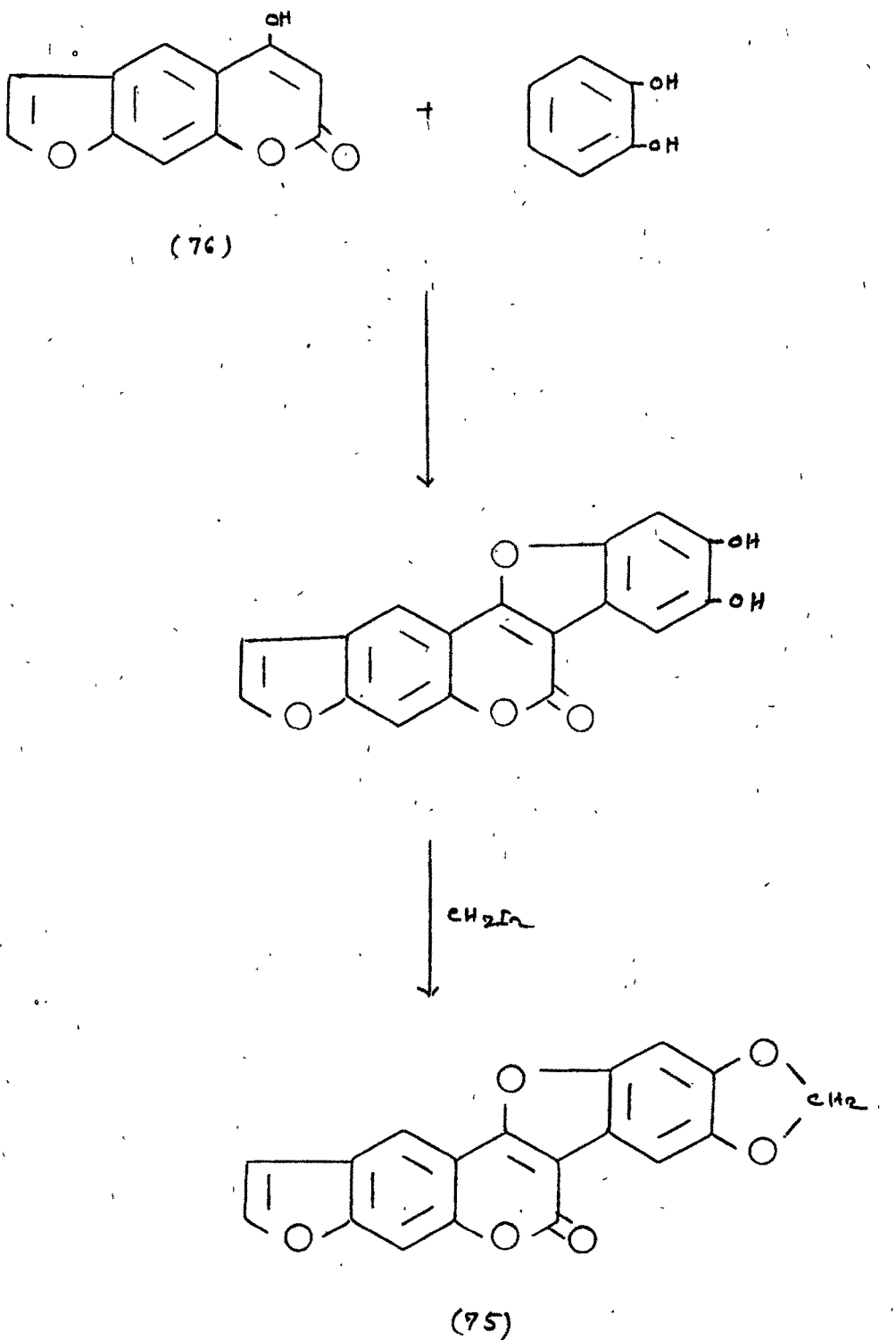
(74)




(75)

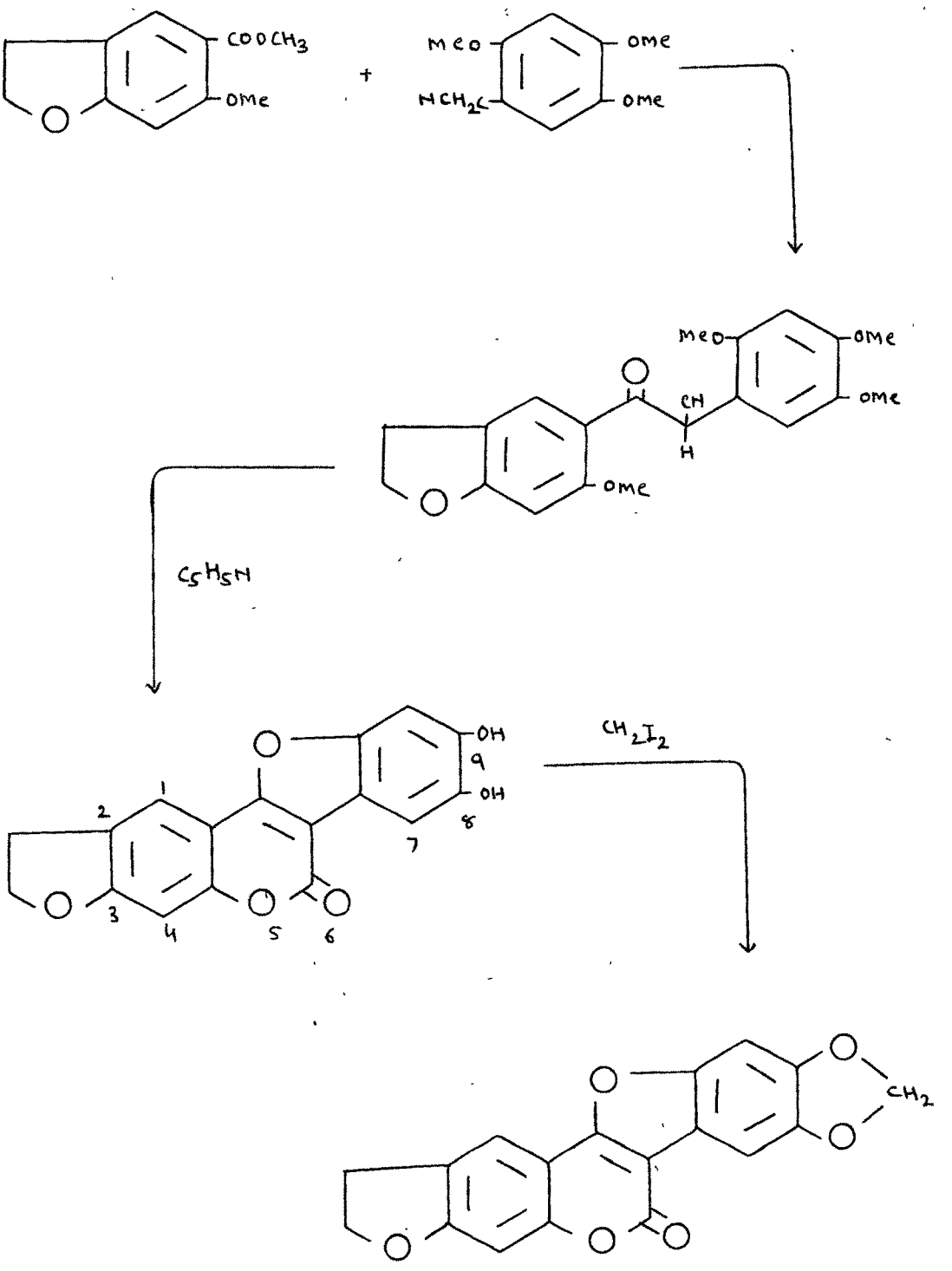
K. Fukai and N. Nakayama[56] synthesised erosnin (75) by dehydrogenative coupling of 5-hydroxy psoralene (76) and catachol in the presence of potassium ferricyanide according to the method of Wanzlick and co-workers followed by methylation with methylene iodide.

Dihydro erosnin[36,45,46] was prepared by appropriate ketonitrile obtained by means of Hoesch reaction. Attempts to bring about dehydrogenation of (77) to erosnin by action of N-Bromo succinimide were unsuccessful.




(76)

(75)


COOCH3
OMe
+
MeO
OMe
NCH2
OMe
MeO
OMe
CH
H
OMe
C5H5N
OH
9
OH
8
7
1
2
3
4
5
6
CH2I2
CH2
(77)

## PRESENT WORK.

From the above review, it is evident that coumestan and furocoumestan, are of great interest and importance, not only because of their occurence in nature, but also due to their valuable estrogenic properties. In continuation of the work carried out on coumestan derivatives in this laboratory by Dholakia and Trivedi and Shaikh and Trivedi, it was therefore thought of interest to study some reaction of hydroxycoumestan derivatives and to build up furan ring on them.

The following furocoumestan derivatives are synthesised by the oxidative coupling of catachol with different 4-hydroxycoumarin derivative, followed by methylation, Claisen migration, cyclisation and dehydrogenation with palladised charcoal.

1. 5'-Methyl-8,9-dimethoxy-furo (2,3-h) coumestan (83).
2. 4,5'Dimethyl-8,9-dimethoxy-furo (3,2-g) coumestan (88).
3. 5'-Methyl-8,9-dimethoxy furo (3,2-f), coumestan (93).

1. Synthesis of 5'-methyl-8,9-dimethoxy-furo (2,3-h)coumestan (83) :

4-Hydroxy-7-allyloxycoumarin (78) was prepared according to Dholakia and Trivedi[57].

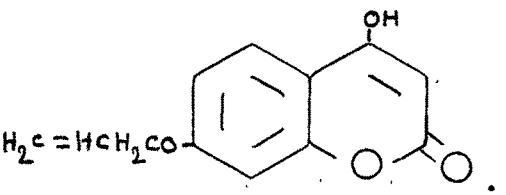
4-Hydroxy-7-allyloxycoumarin (78) on dehydrogenative coupling with catachol in the presence of potassium iodate

gave 3-allyloxy-8,9-dihydroxycoumestan (89) . This compound was high melting, m.p. > 300° and was not soluble in sodium bicarbonate. It also developed green colouration with ferric chloride solution. This on methylation with dimethyl sulphate in the presence of anhydrous potassim carbonate gave 3-allyloxy-8,9-dimethoxycoumestan (80). The I.R. spectra (fig. 1 ) of the compound (80) showed a strong band at 1733 $cm.^{-1}$ (lactonyl > C=0 group) and at 1275 $cm.^{-1}$ (aromatic ether linkage). 3-Allyloxy-8,9-dimethoxycoumestan on Claisen migration in an atmosphere of nitrogen afforded 3-hydroxy-4-allyl-8,9-dimethoxycoumestan (81). I.R. spectram of which showed a band at 1690 $cm.^{-1}$ (lactonyl > C=0 group), 3200 $cm.^{-1}$ (phenolic hydroxyl group). (Fig. 2) 3-Hydroxy-4-allyl-8,9-dimethoxy-coumestan on trituration with conc. sulphuric acid gave 5'-methyl-8,9-dimethoxy-4',5'-dihydro furo (2,3-h)coumestan (82), which underwent dehydrogenation with palladised charcoal to give 5'-methyl-8,9-dimethoxy-furo (2,3-h) coumestan (83), I.R. spectrum of which showed a strong band at 1740 $cm.^{-1}$ (lactonyl >C=0 group), 1260 $cm.^{-1}$ (aromatic ether linkage). (Fig. 3)

2. Synthesis of 4,5 -dimethyl-8,9-dimethoxy-furo (3,2-g) coumestan (88) :

4-Hydroxy-7-allyloxy-8-methyl was prepared according to Dholakia and Trivedi[57].

4-Hydroxy-7-allyloxy-8-methylcoumarin on dehydrogenative coupling with catachol in the presence of potassium iodate gave 3-allyloxy-4-methyl-8,9-dihydroxycoumestan (84).

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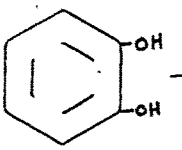
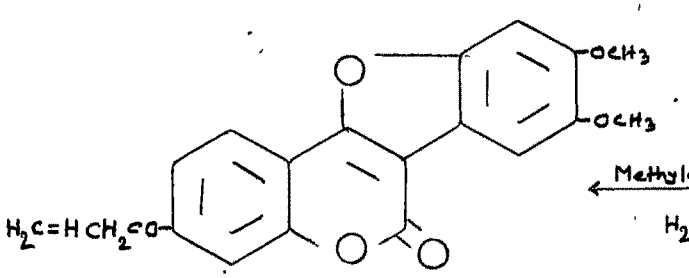
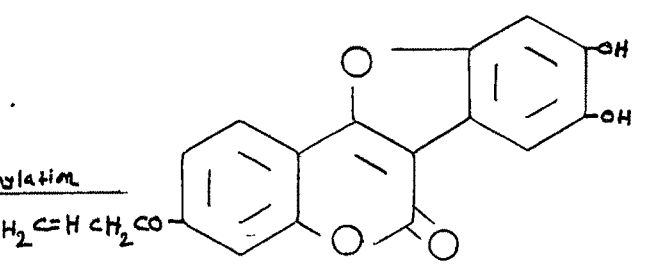



(78)



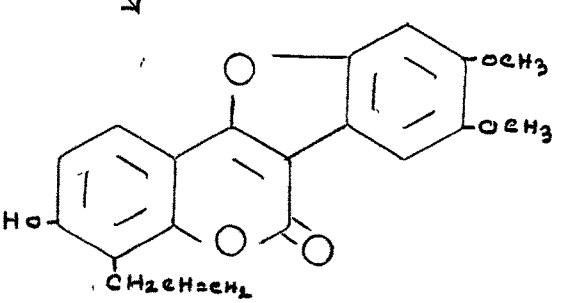

(80)

Methylation

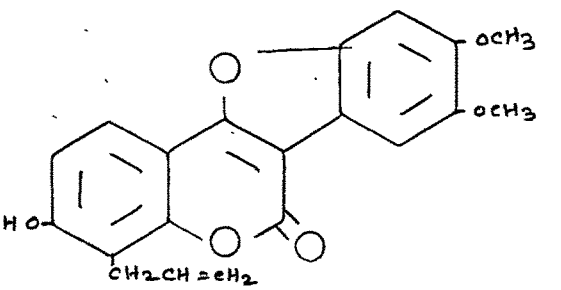



(79)

Dimethyl aniline.

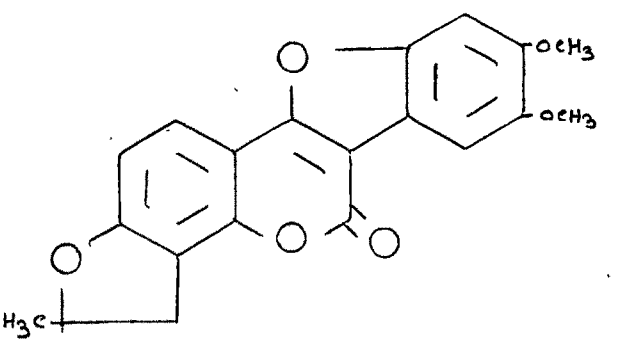



(81)




(81)

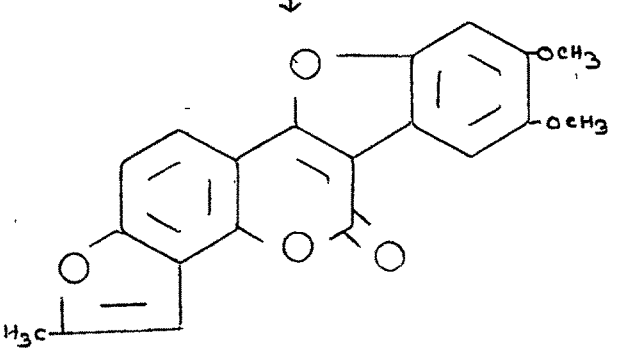
Conc. $H_2SO_4$




(82)

Pd/c

$Ph_2O$



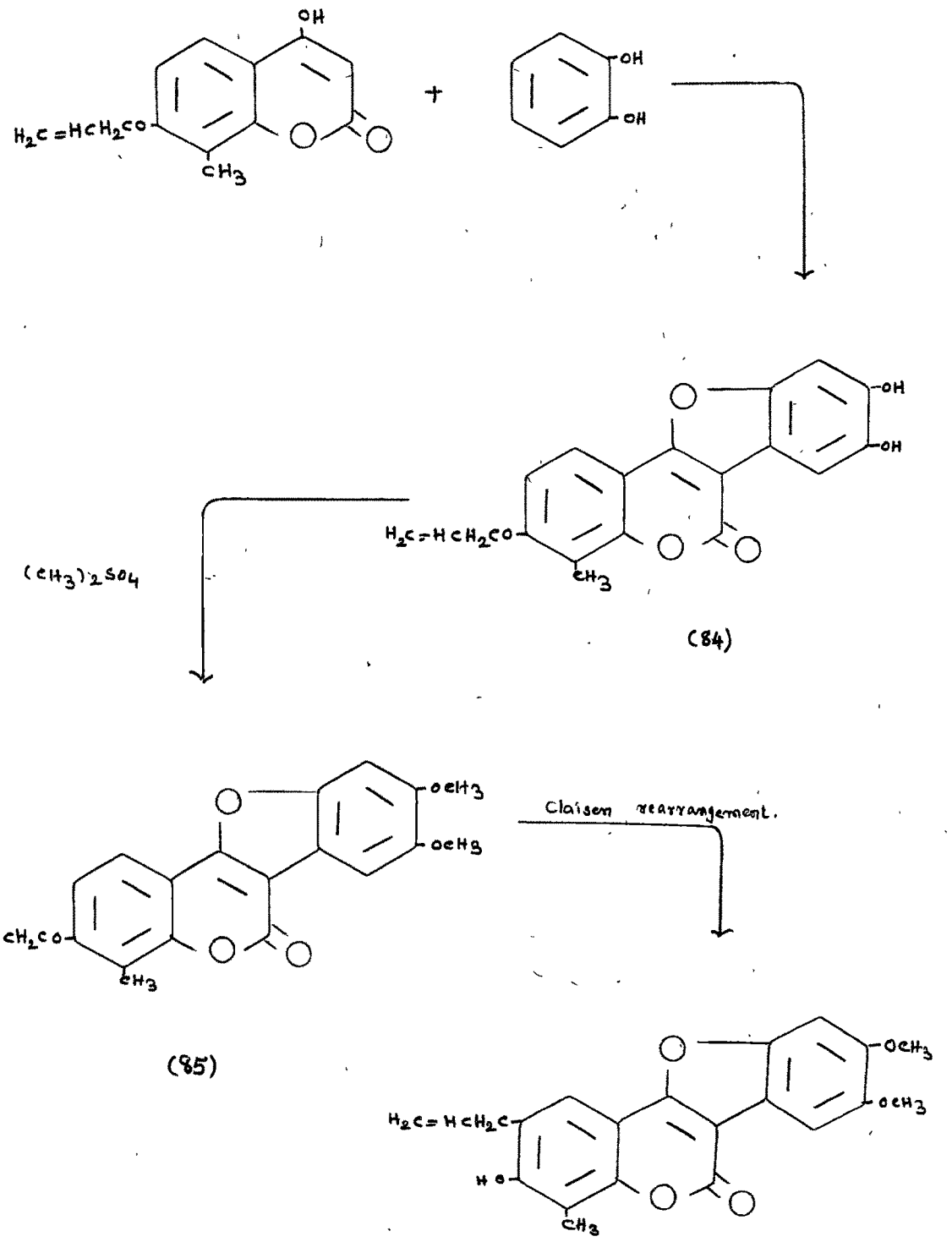

(83)

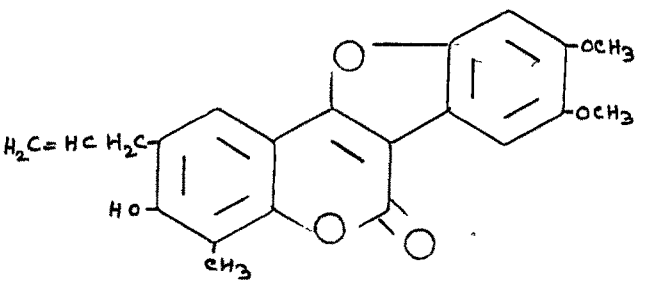
It was insoluble in sodium bicarbonate and developed green colouration with ferric chloride solution. It was not possible to crystallise the compound as it was insoluble in common organic solvent. This compound on methylation with dimethyl sulphate in presence of anhydrous potassium carbonate gave 3-allyloxy-4-methyl-8,9-dimethoxycoumestan (85). (85), on Claisen migration in nitrogen atmosphere gave 3-hydroxy-2-allyl-4-methyl-8,9-dimethoxycoumestan (86). Cyclisation of 3-hydroxy-2-allyl-4-methyl-8,9-dimethoxycoumestan with conc. sulphuric acid afforded 4, 5'-methyl-8,9-dimethoxy-4',5'-dihydro furo (3,2-g) coumestan (87), which on dehydrogenation with palladised charcoal furnished 4,5'-dimethyl-8,9-dimethoxy-furo (3,2-g) coumestan (88). The I.R. spectrum of (88) showed a strong band at 1720 $cm.^{-1}$ (lactonyl >C=O group), 1270 $cm.^{-1}$ (aromatic ether linkage). (Fig. 4)

3. Synthesis of 5'-methyl-8,9-dimethoxy-furo (3,2-f) coumestan (93) :

4-Hydroxy-6-allyloxycoumarin was prepared according to Dholakia and Trivedi[58].

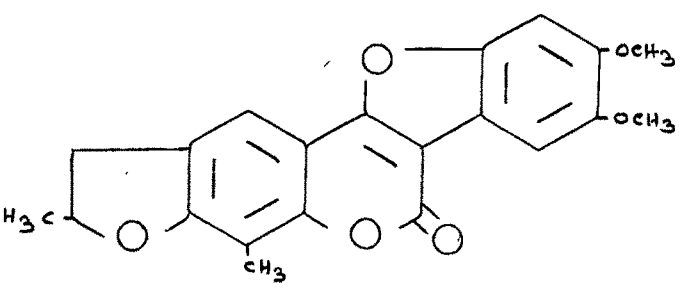
4-Hydroxy-6-allyloxycoumarin on dehydrogenative coupling with catachol in the presence of potassium iodate gave 2-allyloxy-8,9-dihydroxycoumestan (89). It was insoluble in sodium bicarbonate and developed green colouratiom with ferric chloride solution. It is not possible to crystallise as it was insoluble in common organic solvent. 2-Allyloxy-8,9-dihydroxycoumestan on methylation with dimethyl sulphate


OH
$H_2C=HCH_2CO$
$CH_3$
+
OH
OH
OH
OH
$H_2C=HCH_2CO$
$CH_3$
$(CH_3)_2SO_4$
(84)
$OCH_3$
$OCH_3$
$H_2C=HCH_2CO$
$CH_3$
Claisen rearrangement.
(85)
$OCH_3$
$OCH_3$
$H_2C=HCH_2C$
HO
$CH_3$
(86)



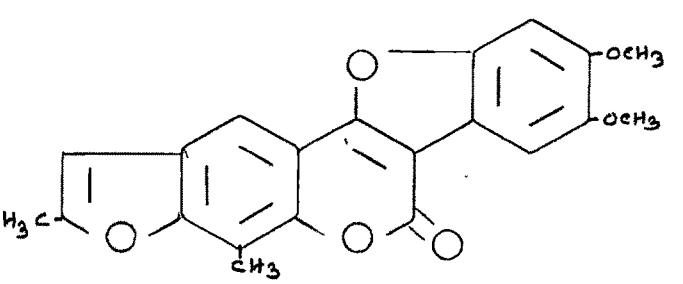

(86)

Conc. $H_2SO_4$




(87)

PdC,
$Ph_2O$.




(88)

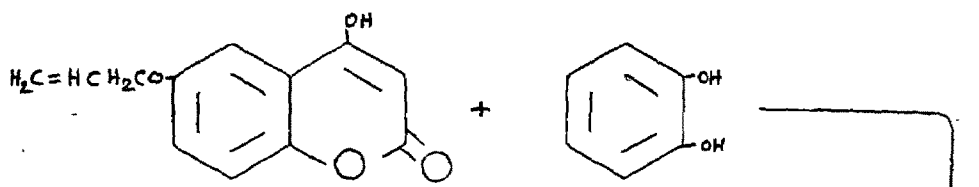
and anhydrous potassium carbonate afforded 2-allyloxy-8,9-dimethoxycoumestan (90), which on Claisen migration gave 2-hydroxy-3-allyl-8,9-dimethoxycoumestan (91). This compound on trituration with conc. sulphuric acid gave 5'-methyl-8,9-dimethoxy-4',5'-dihydro furo (2,3-f) coumestan (92), the NMR spectrum of (92) showed a the following signals : (Fig.5)

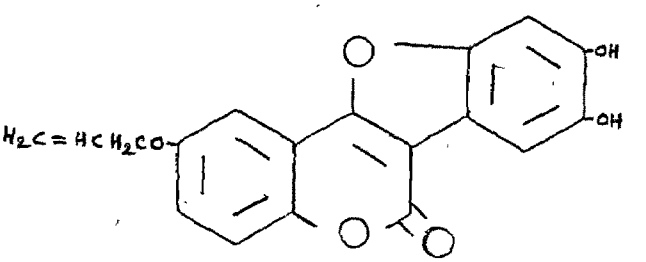
| Chemical shift ( $\delta$ ) ppm. | Coupling constant J (Cps). | Signals | Assignments. |
|---|---|---|---|
| 1.58 | - | Doublet | 3H, $-CH_3$ group at position 5'. |
| 3.0-3.7 | - | Multiplet | 2H, $-CH_2$ group at position 4'. |
| 4.0 | - | Singlet | 6H, Two $-OCH_3$ group at position 8- and 9-. |
| 5.1 | 6.5 | Multiplet | 1H, at position 5'. |
| 6.85 | 9.0 | Doublet | 2H, aromatic proton at position 3. |
| 7.18 | 9.0 | Doublet | 2H, aromatic proton at position 4. |
| 7.32 | - | Singlet | 1H, aromatic proton at position 10. |
| 7.45 | - | Doublet | 1H, aromatic proton at position 7. |

The two proton doublet at $\delta$ 6.85 and $\delta$7.18 confirms that the two aromatic proton at position 3 and 4- are free to

couple and that the Claisen migration has taken place on position 1-. If migration had taken place at position 3- and cyclised as in structure (92a), the aromatic proton at 1- and 4-position would have appeared as singlets.

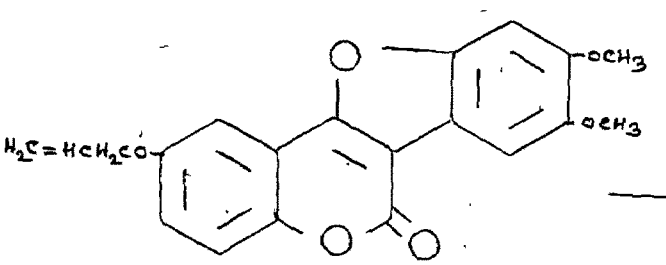
5'-Methyl-8,9-dimethoxy-4',5'-dihydro furo (2,3-f) coumestan (92) on dehydrogenation with palladised charcoal in diphenyl ether furnished 5'-methyl-8,9-dimethoxy-furo (3,2-f) coumestan (93).





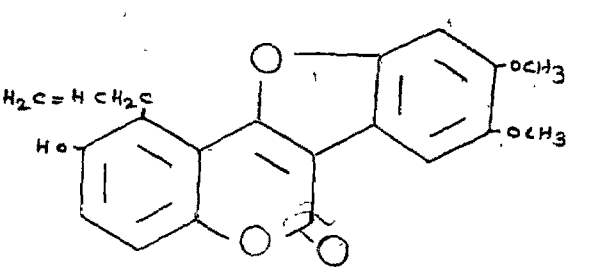
(89)

$(CH_3)_2SO_4$

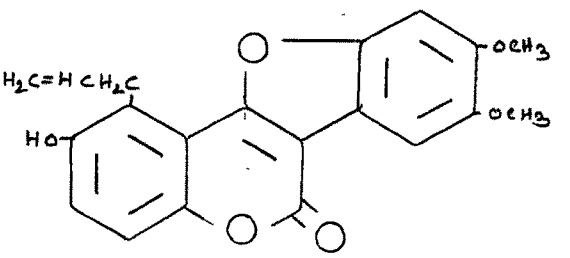


(90)

Claisen rearrangement.

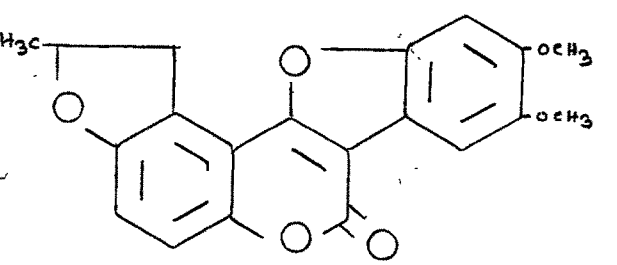


(91)



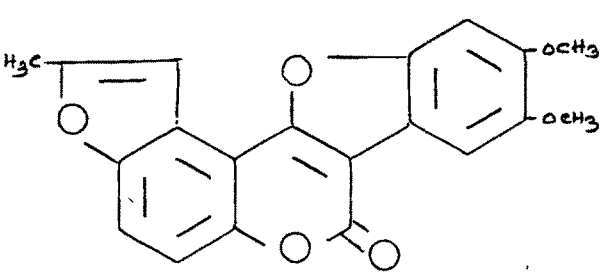

(91)

Conc. $H_2SO_4$

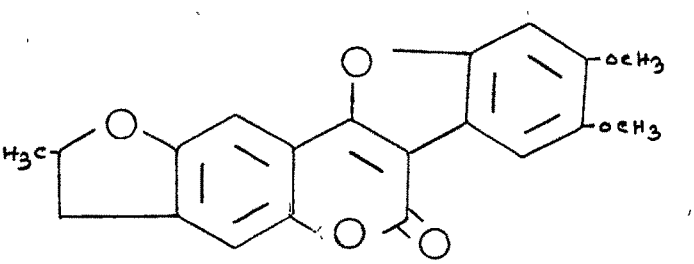



(92)

Pd/c , $Ph_2O$




(93)




(92a)

## E X P E R I M E N T A L.

I.R.spectra were determined with Perkin-Elmer 457 Model Spectrophotometer in nujol.

NMR spectra were recorded on Varian A-60 Model using TMS as internal indicator. Solvent $CDCl_3$ (Fig. 5)

The Ultra-Violet absorption Spectra were measured with Beckmann DU-2 Model Spectrophotometer.

Synthesis of 5'-methyl-8,9-dimethoxy-furo (2,3-h) coumestan (83) : Dehydrogenative coupling of 4-hydroxy-7-allyloxy-coumarin with catachol : 3-Allyloxy-8,9-dihydroxycoumestan(79) :

4-Hydroxy-7-allyloxycoumarin was prepared according to Dholakia and Trivedi[56].

3-Allyloxy-8,9-dihydroxycoumestan (79) :

To the solution of 4-hydroxy-7-allyloxycoumarin (1 g.),catachol,(0.5 g.), and sodium acetate (2 g.) in acetone-water (25 ml.; 1 : 1), a solution of potassium iodate (0.5 g.) and sodium acetate (1 g.) in water (10 ml.) was added slowly with constant stirring. It was allowed to stand for 1 hr. The separated product was filterdd, washed with sodium bicarbonate. The product was insoluble in sodium bicarbonate and developed green colouration with ferric chloride solution. It was not possible to crystallise the compound as it was insoluble in common organic solvent, m.p. 300°. Yield 0.8 g.

Methylation of 3-allyloxy-8,9-dihydroxycoumestan : 3-Allyloxy-8,9-dimethoxycoumestan (80) :

A mixture of 3-allyloxy-8,9-dihydroxycoumestan (2 g.) dimethyl sulphate (1.6 g.) and anhydrous potassium carbonate (4 g.) in dry acetone (100 ml.) were refluxed on a water bath for 8 hr. After the evaporation of acetone, the residue was treated with water. The product was filtered, washed with dilute sodium hydroxide solution and crystallisdd from acetic acid, m.p. 198°. Yield 1.8 g.

Analysis : Found : C, 68.47 ; H, 4.82 %.

$C_{20}H_{16}O_6$ : requires : C, 68.19 ; H, 4.55 %.

I.R.spectrum : 1733 $cm.^{-1}$ (lactonyl > C=O group), 1275 $cm.^{-1}$ (aromatic ether linkage).

Claisen migration of 3-allyloxy-8,9-dimethoxycoumestan : 3-Hydroxy-4-allyl-8,9-dimethoxycoumestan (81) :

3-Allyloxy-8,9-dimethoxycoumestan (2 g.) was refluxed in dimethyl aniline (10 ml.) under nitrogen atmosphere for 6 hr. The reaction mixture was cooled andp poured into ice and conc. hydrochloric acid. The solid which separated was filtered, washed with water and treated with dilute sodium hydroxide solution. It was again filtered, acidified and crystallised from acetic acid, m.p. 258°. Yield 1.5 g.

Analysis : Found : C, 67.90 ; H, 4.44 %

$C_{20}H_{16}O_6$ : requires : C, 68.19 ; H, 4.55 %.

I.R.spectrum : 1690 $cm.^{-1}$ (lactonyl >C=O group), 3200 $cm.^{-1}$ (aromatic hydroxy group).

Cyclisation of 3-hydroxy-4-allyl-8,9-dimethoxycoumestan : 5'-Methyl-8,9-dimethoxy-4',5'-dihydro furo (2,3-h) coumestan(82) :

3-Hydroxy-4-allyl-8,9-dimethoxycoumestan (0.7 g.) was triturated with conc. sulphuric acid (4 ml.) for 10 minutes. The reaction mixture was poured into crushed ice and water. The separated product was filtered, washed with dilute sodium hydroxide solution and dried. It was purified by passing a chloroform solution of it over a short column of alumina. It crystallised from chloroform-petroleum ether, m.p. 203°. Yield 0.5 g.

Analysis : Found : C, 67.72 ; H, 4.72 %

$C_{20}H_{16}O_6$ : requires : C, 68.19 ; H, 4.55 %.

Dehydrogenation of 5'-methyl-8,9-dimethoxy-4',5'-dihydro furo (2,3-h) coumestan : 5'-Methyl-8,9-dimethoxy-furo (2,3-h) coumestan (83) :

5'-Methyl-8,9-dimethoxy-4',5'-dihydro furo (2,3-h) coumestan (0.8 g.) was refluxed with diphenyl ether (6 ml.) in the presence of palladised charcoal (0.6 g. ; 10 %) for 20 hr. The reaction mixture was filtered hot and allowed to cool. To the cooled solution, petroleum ether was added and the separated product was filtered. It was purified by passing a benzene solution of it over a shat column of alumina. It crystallised from benzene-petroleum ether, m.p. 253°. Yield 0.5 g.

Analysis : Found : C, 68.28 ; H, 3.93 %

$C_{20}H_{14}O_6$ : requires : C, 68.67 ; H, 4.00 %.

I.R.spectrum : 1740 $cm^{-1}$ (lactonyl > C=O group), 1260 $cm^{-1}$ (aromatic ether linkage).

$\lambda^{Methanol}_{Max.}$ 242 nm (log e 4.57), 340 nm (log e 4.40).

Synthesis of 4,5'-dimethyl-8,9-dimethoxy-furo (3,2-g)coumestan (88) : Dehydrogenative coupling of 4-hydroxy-7-allyloxy-8-methylcoumarin with catachol :

4-Hydroxy-7-allyloxy-8-methylcoumarin was prepared according to Dholakia and Trivedi[56].

3-Allyloxy-4-methyl-8,9-dihydroxycoumestan (84) :

To the solution of 4-hydroxy-7-allyloxy-8-methyl-coumarin (1 g.), catachol (0.5 g.) and sodium acetate (2 g.) in acetone-water (25 ml.; 1 : 1), a solution of potassium iodate (0.5 g.) and sodium acetate (1 g.) in water (10 ml.) was added slowly with constant stirring. It was allowed to stand for 1 hr. The reaction mixture was worked up as before. The product was insoluble in sodium bicarbonate and developed green colouration with ferric chloride solution. It was possible to crystallise the compound as it was insoluble in common organic solvent, m.p. 300°. Yield 0.5 g.

Methylation of 3-allyloxy-4-methyl-8,9-dihydroxycoumestan :

3-Allyloxy-4-methyl-8,9-dimethoxycoumestan (85) :

A mixture of 3-allyloxy-4-methyl-8,9-dihydroxy-coumestan (2 g.), dimethyl sulphate (1.6 g.) and anhydrous potassium carbonate (4 g.) in dry acetone (100 ml.) were refluxed on a water bath for 8 hr. The reaction mixture was worked up as usual. The product crystallised from acetic acid, m.p. 212°. Yield 1.8 g.

Analysis : Found : C, 68.42 ; H, 5.15 %

$C_{21}H_{18}O_6$ : requires : C, 68.85 ; H, 4.92 %.

Claisen rearrangement of 3-allyloxy-4-methyl-8,9-dimethoxy-coumestan : 3-Hydroxy-2-allyl-4-methyl-8,9-dimethoxycoumestan (86) :

3-Allyloxy-4-methyl-8,9-dimethoxycoumestan (2 g.) was refluxed in dimethyl aniline (10 ml.) in the nitrogen atmosphere for 6 hr. The reaction mixture was worked up as usual. The product crystallised from acetic acid, m.p. 247°. Yield 1.5 g.

Analysis : Found : C, 69.07 ; H, 5.60 %

$C_{21}H_{18}O_6$ : requires : C, 68.85 ; H, 4.92 %.

Cyclisation of 3-hydroxy-2-allyl-4-methyl-8,9-dimethoxy-coumestan : 4,5'-Dimethyl-8,9-dimethoxy-4',5'-dihydro furo (3,2-g) coumestan (87) :

3-Hydroxy-2-allyl-4-methyl-8,9-dimethoxycoumestan (0.8 g.) was triturated with conc. sulphuric acid (4 ml.) for 10 minutes. The reaction mixture was poured into crushed ice and water. The product was filtered, washed with dilute sodium hydroxide solution and crystallised from acetic acid,

m.p. 265°. Yield 0.5 g.

Analysis : Found : C, 68.55 ; H, 4.60 %

$C_{21}H_{18}O_6$ : requires : C, 68.85 ; H, 4.92 %.

Dehydrogenation of 4,5'-dimethyl-8,9-dimethoxy-4',5'-dihydro-furo (3,2-g) coumestan : 4,5'-Dimethyl-8,9-dimethoxy-furo (3,2-g) coumestan (88) :

4,5'-Dimethyl-8,9-dimethoxy-4',5'-dihydro furo (3,2-g) coumestan (0.8 g.) was refluxed with diphenyl ether (6 ml.) in the presence of palladised charcoal (0.6 g.; 10 %), for 20 hr. The reaction mixture was worked up as before. The compound was crystallised from acetic acid, m.p. 288°. Yield 0.5 g.

Analysis : Found : C, 69.31 ; H, 4.15 %

$C_{21}H_{16}O_6$ : requires : C, 69.23 ; H, 4.39 %.

I.R.spectrum : 1720 $cm.^{-1}$ (lactonyl > C=O group), 1270 $cm.^{-1}$ (aromatic ether linkage).

$\lambda^{Methanol}_{Max.}$ 286 nm (log e 3.81), 350 nm (log e 4.27).

Synthesis of 5'-methyl-8,9-dimethoxy-furo (3,2-f) coumestan (93) : Dehydrogenative coupling of 4-hydroxy-6-allyloxy-coumarin with catachol : 2-Allyloxy-8,9-dihydroxycoumestan(89):

4-Hydroxy-6-allyloxycoumarin was prepared according to Dholakia and Trivedi[57].

To the solution of 4-hydroxy-6-allyloxycoumarin

(1 g.), catachol (0.5 g.) and sodium acetate (2 g.) in acetone -water (25 ml.; 1:1), a solution of potassium iodate (0.5 g.) and sodium acetate (1 g.) in water (10 ml.) was added slowly with constant stirring. It was allowed to stand for 1 hr. The reaction mixture was worked up as before. The product was insoluble in sodium bicarbonate solution and developed green colouration with ferric chloride solution. It was not possible to crystallised the compound as it was insoluble in common organic solvent, m.p. >300°. Yield 0.8 g.

Methylation of 2-allyloxy-8,9-dihydroxycoumestan : 2-Allyloxy-8,9-dimethoxycoumestan (90) :

A mixture of 2-allyloxy-8,9-dihydroxycoumestan (2 g.) dimethyl sulphate (1.6 g.) and anhydrous potassium carbonate (4 g.) in dry acetone (100 ml.) were refluxed in a water bath for 8 hr. The reaction mixture was worked up as usual. The product crystallised from acetic acid, m.p. 176°. Yield 1.5 g.

Analysis : Found : C, 67.75 ; H, 4.82 %

$C_{20}H_{16}O_6$ : requires : C, 68.19 ; H, 4.55 %.

I.R. spectrum : 1730 $cm^{-1}$ (lactonyl > C=O group), 1270 $cm^{-1}$ (aromatic ether linkage).

Claisen rearrangement of 2-allyloxy-8,9-dimethoxycoumestan : 2-Hydroxy-1-allyl-8,9-dimethoxycoumestan (91) :

2-Allyloxy-8,9-dimethoxycoumestan (2 g.) was refluxed in dimethyl aniline (10 ml.) in nitrogen atmosphere

for 6 hr. The reaction mixture was worked up as usual. The product crystallised from acetic acid, m.p. 222°. Yield 1.8 g.

Analysis : Found : C, 67.81 ; H, 4.43 %

$C_{20}H_{16}O_6$ : requires : C, 68.19 ; H, 4.55 %.

I.R. spectrum : 1705 $cm.^{-1}$ (lactonyl > C=O group), 1265 $cm.^{-1}$ (aromatic ether linkage), and a broad band at 3280 $cm.^{-1}$ (aromatic hydroxyl group).

Cyclisation of 2-hydroxy-1-allyl-8,9-dimethoxycoumestan : 5-Methyl-8,9-dimethoxy-4,5-dihydroxy furo (3,2-f) coumestan (92)

2-Hydroxy-1-allyl-8,9-dimethoxycoumestan (0.8 g.) was triturated with conc. sulphuric acid (4 ml.) for 10 minutes. The reaction mixture was poured into crushed ice and water. The product was filtered, washed with dilute sodium hydroxide solution and crystallised from acetic acid, m.p. 239°. Yield 0.5 g.

Analysis : Found : C, 67.94 ; H, 4.36 %

$C_{20}H_{16}O_6$ : requires : C, 68.19 ; H, 4.55 %.

I.R. spectrum : 1720 $cm.^{-1}$ (lactonyl > C=O group), 1270 $cm.^{-1}$ (aromatic ether linkage).

Dehydrogenation of 5'-methyl-8,9-dimethoxy-4',5'-dihydro furo (3,2-f) coumestan : 5'-Methyl-8,9-dimethoxy-furo (3,2-f) coumestan (93) :

5'-Methyl-8,9-dimethoxy-4',5'-dihydro furo (3,2-f) coumestan (0.8 g.) was refluxed with diphenyl ether (6 ml.) in the presence of palladised charcoal (0.6 g.; 10 %) for

20 hr. The reaction mixture was worked up as before. The compound crystallised from acetic acid, m.p. 262°. Yield 0.5 g.

Analysis : Found : C, 68.63 % H, 3.99 %

$C_{20}H_{14}O_6$ : requires : C, 68.57 ; H, 4.00 %.

I.R. spectrum : 1710 $cm^{-1}$ (lactonyl > C=O group), 1266 $cm^{-1}$ (aromatic ether linkage).

$\lambda^{\text{Methanol}}_{\text{Max.}}$ 248 nm (log e 4.30), 282 nm (log e 4.01), 306 nm (log e 3.92) and at 355 nm (log e 4.47).

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