PHOTODYNAMICALLY ACTIVE PLANT PRODUCTS

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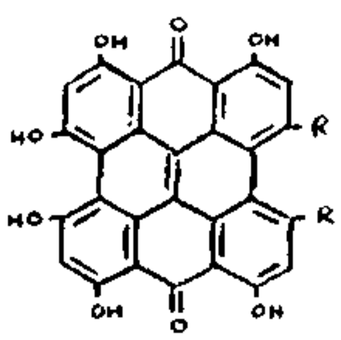
PHOTODYNAMIC COMPOUNDS

(*a*) ANTHRONE GROUP

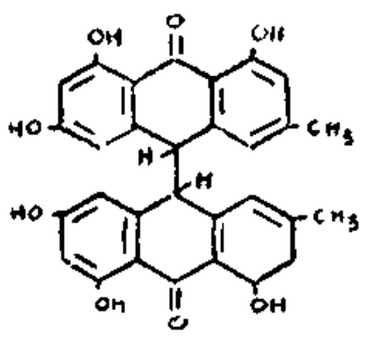
AT the beginning of this century a study by von Tappeiner[1] led to the discovery which is known as "*photodynamic effect*". According to him, not only micro-organisms but even higher animals could be made sensitive to light by means of fluorescent colouring matters. For example, when eosin is fed to animals such as white rats or rabbits, and they are then exposed to light, they become excited ; their skin reddens and oedema sets in. Even after illumination has been stopped, inflammation of the skin develops. These observations explained certain phenomena which went under the names '*hypericism*' and '*fagopyrism*' and were known for a long time. These terms have been used for the effects produced on animals when they ate plants of the genera *Hypericum* (St. John's Wort) and *Fagopyrum* (Buck-wheat). The phenomena were very similar to the photodynamic effect and were obviously due to some fluorescent chemicals in the plants. A detailed study by Brockmann and his coworkers[2] over a long period led to the isolation and elucidation of the constitution of the concerned photodynamic pigments. *Hypericum* plants contain hypericin (I) as the main component, along with *pseudo*hypericin (II). These are remarkably large molecules containing condensed benzene rings and are derived from widely distributed anthraquinone derivatives such as emodin (III) by simple reactions taking place in the plants. Fagopyrin (IV), another related compound, was isolated from buck-wheat. The main result of their work is that these photodynamically active plant pigments are derivatives of hexahydroxy helianthrone (V) containing other substituents. They are synthesized in the plants by dehydrogenation of the corresponding substituted dianthrones (VI). These dianthrones seem to be fairly widely occurring. Actually di-emodin anthrone (VI) is found as its diglycoside in Frangula bark and di-rhein anthrone glycosides (sennosides) are present in senna leaves. These are well-known plant purgatives.



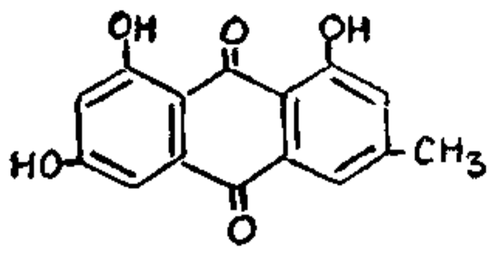
(I) , R = CH_3

(II) , R = $-CH(OH)-CH_3$

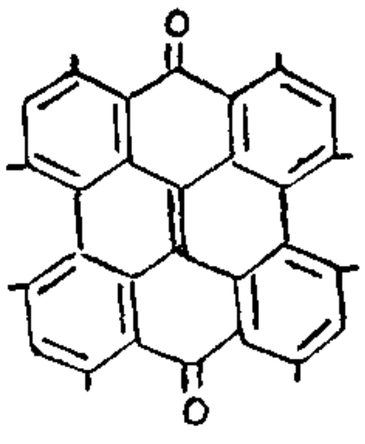
(IV) , R = $-CH_2-(C_{14}H_{11}ON)$



(VI)

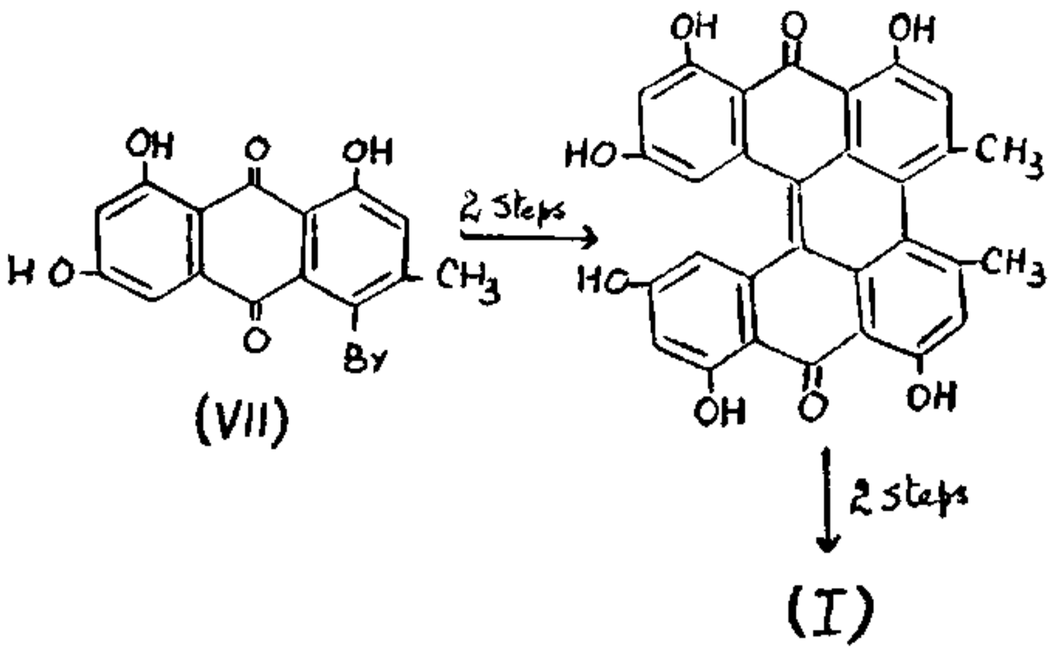


(III)



(V)

Hypericin (*I*) has been synthesised by Brockmann[2] from trimethyl ether of 1-bromo emodin (VII), which was earlier prepared by Adams and Jacobsen.[3] It (VII) was converted into hypericin as shown below.

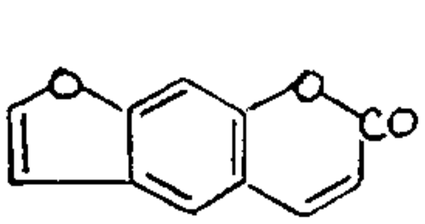


(VII)

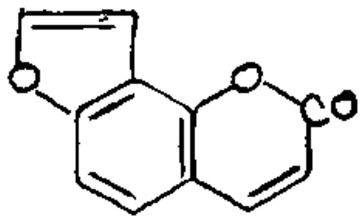
(*b*) *Psoralen Group*

There is another group of compounds which do not seem to produce such marked ill-effects but are still found to be photodynamically active and have been used for the treatment of certain skin diseases. For a long time plants containing furanocoumarins have been used in different parts of the world for the treatment of vitiligo, commonly known as leucoderma. The most important plant materials which have been frequently used in the form of their preparations are the seeds of *Psoralea corylifolia*, *Ammi visnaga*. *Ammi majus* and *Pongamia glabra*,

Psoralea corylifolia, the most important species of the genus *Psoralea*, belongs to the family *Leguminoseæ*. The seeds of this plant have been in use in Indian medicine from ancient times and according to some physicians they are useful in the treatment of diseases of the skin such as leucoderma and psoriasis. The drug is prescribed both for local application and for oral administration. It was as early as 1923 when a careful examination of the seeds was made in the Calcutta School of Tropical Medicine and an oleo-resin fraction was prepared for clinical trials. The results of its local application on leucodermic spots were satisfactory, and created considerable amount of interest in the further study of the drug. The active constituents, psoralen (VIII) and *iso*-psoralen (IX), were isolated in a crystalline condition by Jois *et al.*[4]; later, Rangaswami and Seshadri[5] gave a convenient method for the isolation of the mixture of psoralen and *iso*-psoralen. Recently, Khastgir *et al.*[6] further improved this method. This mixture has been used successfully in the treatment of leucoderma.[7] It is administered orally and applied locally at the leucodermic spots, which are then exposed to sunlight or U.V. light.



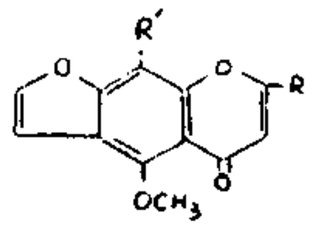
(VIII)



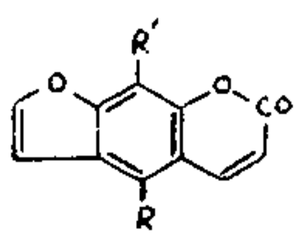
(IX)

Another important drug which has been given a prominent position in the treatment of leucoderma is the seeds of *Ammi visnaga* L. Extracts of this plant, under the name khellah or chellah, have been used for centuries as a home remedy to relieve spasms of all kinds and also as a cure for leucoderma.[8] The earliest work in the direction of chemical investigation of this drug was done by Spath and Gruber.[9] They obtained kellin (X) as the major product of the ether extract of the seeds of the plant, along with visnagin (XI) and kellol glycoside (XII). These are γ-pyrone derivatives. Later fractions of the ether extract of the drug which are more active, contain coumarin derivatives.

It was later discovered that the fruits of *Ammi majus*, a closely related plant, are far more useful for leucoderma whereas *Ammi visnaga*, and particularly kellin, have been useful for the treatment of heart diseases. *Ammi majus* was originally grown in Egypt. It is also grown in India as an ornamental plant in gardens. The efficacy of its seeds in the treatment of leucoderma was first observed in 1948 in Egypt and later in France. Its active constituents were tested either in the form of tablets or as extracts and encouraging results were reported. Further, the isolation of the active principles and their identification as xanthotoxin (XIII), imperatorin (XIV) and bergapten (XV) by Falmy and Abushady[10] and by Schönberg and Sina[11] opened a new line of investigation on the therapeutic efficacy of these coumarin compounds in the cure of leucoderma. Several other plants contain these photodynamically active compounds. Among these are *Ficus carica*, *Angelica officinalis*, *Pastinaca sativa*, *Luvanga scandens*, *Aegle marmelos*, *Heracleum mantegazianum* and *Ruta graveolens*.



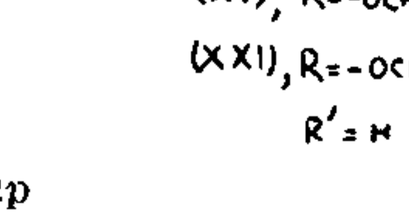
(X), R = -CH₃; R = -OCH₃
(XI), R = -CH₃; R = H
(XII), R = -CH₂OGl; R = H



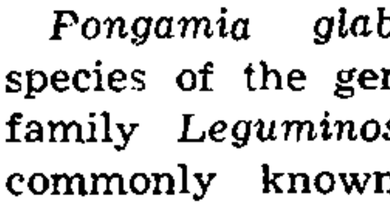
(XIII), R = H; R = -OCH₃
(XIV), R = H; R = -OCH₂-CH=C(CH₃)₂
(XV), R = -OCH₃, R = H
(XXI), R = -OCH₂-CH(O)-C(CH₃)₂, R = H

(c) *Flavone Group*

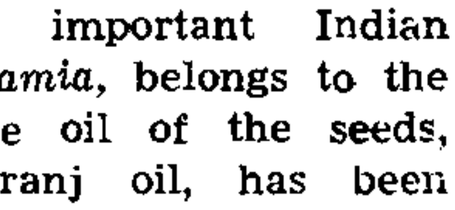
Pongamia glabra, the important Indian species of the genus *Pongamia*, belongs to the family *Leguminoseæ*. The oil of the seeds, commonly known as karanj oil, has been well known as an efficient home remedy for the treatment of common ailments and skin diseases like leucoderma.[12] Chemical examination of the seed oil (from *Pongamia glabra*) was first reported by Limaye,[13] who isolated a bitter crystalline furanoflavone and named it karanjin (XVI). It exerts appreciable curative



(XVII)



(XVI), R = -OCH₃, R = H
(XVIII), R = H; R = -OCH₃



(XIX), R = -OCH₃
(XX), R = H

effect in skin diseases and is free from highly irritating and inflammatory effects of coumarin

compounds. Recently many other compounds have been isolated and their constitutions established.[14,15] These are pongamol (XVII), kanjone (XVIII), pongapin (XIX) and pongaglabrone (XX).

Chemical Constitution and Photodynamic Activity

Skin photosensitization is at present the best known property of furanocoumarins. Photodermatites occurs when the skin comes in contact with plants or vegetable products and is then exposed to sunlight or U.V. light. Further, erythemas of various degrees, followed by pigmentation, appear after a latent period. As early as 1938, Kuske[16] studied some of these cases and found that, besides plant extracts, two pure coumarins, oxypeucedanin (XXI) and bergapten, were also photodynamically active.

Recently Musajo and Rodighiero[17] have studied the photosensitizing effect of psoralen (VIII) and have tried to establish the relationship between structure and photodynamic property in coumarins. They used the ethanolic solution of these compounds on 2–4 $cm.^2$ size areas of the human skin and then exposed them to sunlight or U.V. light. They also performed quantitative tests by determining the minimum time of irradiation, necessary to produce erythema on the skin, taking psoralen as a standard. Pathak *et al.*[18] have done experiments on guinea-pigs by applying 1000 μg. of each furanocoumarin on the skin, which was irradiated for 45 minutes with a U.V. lamp placed at a distance of 12–15 cm. The results of their investigations led to the following conclusions:

(*i*) Photodynamic activity is fundamentally linked to the furanocoumarinic ring system and seems to depend upon the position of the furan ring; in fact, linear furanocoumarinic structure (as found in psoralen) is more effective than the angular one (as found in angelicin). (*ii*) Substitution in the condensed benzene ring reduces the activity. Groups like $-OCH_3$, $-CH_3$, $-COCH_3$, etc., decrease the activity, while $-OH$, $-NH_2$, $-NO_2$, etc., annul the activity of the parent compounds.

The widespread occurrence of such compounds like bergapten, xanthotoxin, etc., gives an explanation for the frequent occurrence of photodermatites of vegetable origin. It was known quite early that celery and parsley cause dermatites on the hands of the people who handle them, but the reason was clear only when Musajo and Rodighiero (*loc. cit.*) isolated bergapten from them.

The physiological properties of furanocoumarins have been compared with other photodynamically active compounds like hæmatoporphyrin, hypericin and fagopyrin and it was shown that furanocoumarins exhibit a different type of photodynamic activity. For instance, the former group of compounds photo-oxidize α-terpinene, and blood serum but are not active if painted on the skin. Furanocoumarins, on the contrary, do not influence the photo-oxidation of α-terpinene and do not oxidize blood serum proteins to an appreciable extent but are active when painted on the skin. Both groups on intradermical injection provoke dermatites, erythema and later pigmentation. So it is clear that furanocoumarins are a group of photodynamic compounds having a peculiar type of activity and their effect on the skin is not a photo-oxidation of proteic substrates. Recently, Rashid and Aggrawala[19] have shown that psoralen in aqueous ethanolic solution gives degradative products which inactivate –SH group as indicated by the inhibition of succinic dehydrogenase of rat kidney and reversal of thiourea inhibition of potato tyrosinase when exposed to solar irradiations. This inactivation has been considered to be related to the role of psoralen in the production of pigments. Previously it was thought that furanocoumarins could probably cause light cancer but recently Pathak *et al.*[18] have found that they are not dangerous in this way.

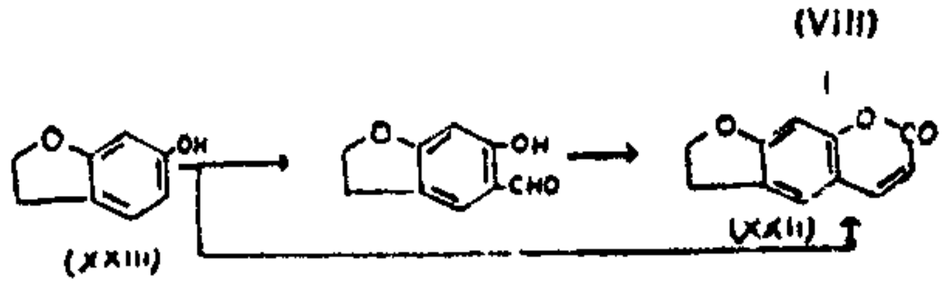
Synthesis in the Furanopyrone Group

In view of the interest on the possible pigment stimulating properties of these compounds in the treatment of leucoderma, there was need for a convenient synthesis in order to produce them on a large scale for study and use in the cure of leucoderma.

Coumarin Group

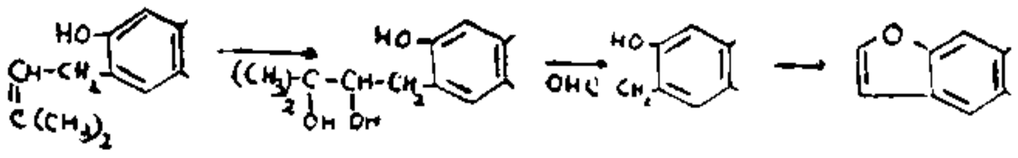
(*a*) *Linear Furanocoumarins*

Psoralen (VIII) is the most active member of the group and is present in *Psoralea corylifolia* and in several other plant sources. It has earlier been synthesized by four different routes. In the first three syntheses[20-22] dihydropsoralen (XXII) has been obtained from 6-hydroxycoumaran (XXIII) by different ways as shown below. The dihydro compound was converted

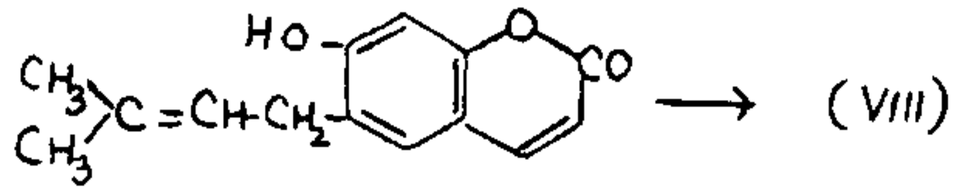


into psoralen in poor yield by treating it with Pd-C catalyst.

Aneja *et al.*[23] made a general study of the origin of the furan ring in natural products and concluded that a prenyl unit underwent oxidation at the double bond, followed by ring closure. They modified this to develop a new and convenient method of furan ring closure. It consists of the Claisen migration of an allyl ether and the subsequent oxidation of the allylic double bond by ozone. The ozonide can be decomposed by catalytic hydrogenation. Raizada *et al.*[24] used osmium tetroxide instead of ozone for the oxidation of allylic double bond. The diol so obtained was degraded with potassium periodate. The acetaldehyde intermediate in both the cases was cyclised by means of polyphosphoric acid. These general features are brought out in the following formulæ.

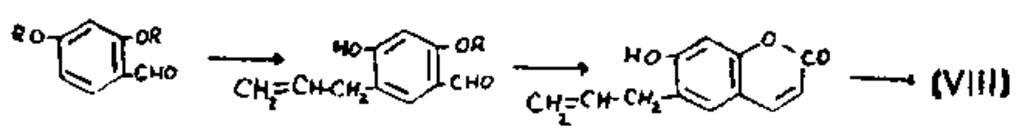


Based on these ideas Aneja *et al.*,[23] obtained psoralen starting from demethylsuberosin (XXIV), a naturally occurring coumarin.



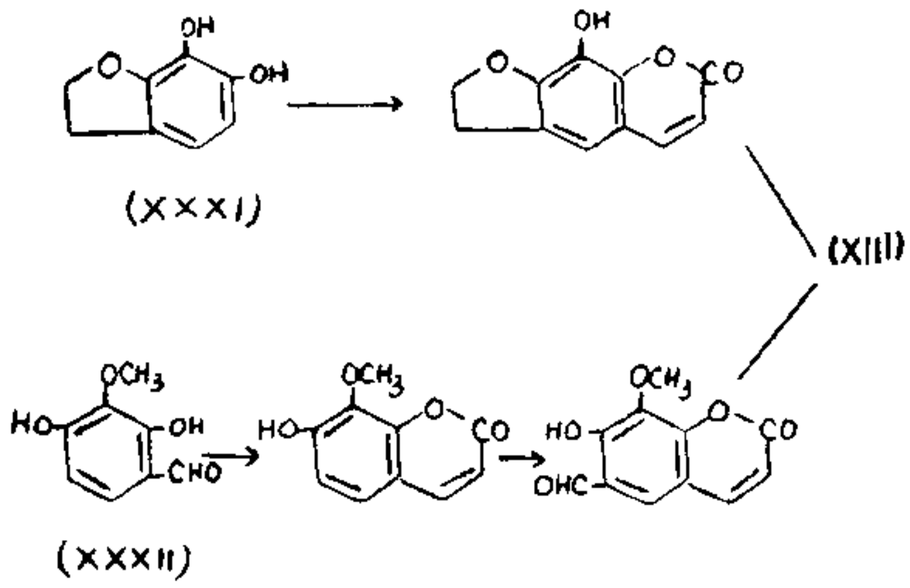
(XXIV)

For purely synthetic purposes, a simple allyl group should be equally good. 6-Allyl umbelliferone (XXV) could therefore be the most satisfactory for this purpose. As there is no simple method for the preparation of this compound from umbelliferone, an alternative procedure[25] starting from β-resorcylaldehyde (XXVI) has now been worked out quite satisfactorily. It could be partially allylated[26] to 4-0-allyl-β-resorcylaldehyde (XXVII). This, however, could not be used directly for Claisen migration because it has been shown to go into the active 3-position. Therefore, a modified procedure has to be employed in which the ortho-hydroxyl is protected before Claisen migration. Benzyl and tosyl groups were found to be unsatisfactory for this purpose; methyl group was, therefore, used. 4–0-Allyl-β-resorcylaldehyde (XXVII) was methylated using dimethyl sulphate and potassium carbonate. The allyl methyl ether (XXVIII) was subjected to Claisen migration when 5-allyl-4-hydroxy-2-methoxybenzaldehyde (XXIX) was obtained. Demethylation using $AlCl_3$-ether gave 5-allyl-2, 4-dihydroxy benzaldehyde (XXX) which on Perkin condensation yielded 7-hydroxy-6-allylcoumarin (XXV). It was subjected to ozonolysis and the intermediate acetaldehyde was cyclised by means of polyphosphoric acid to psoralen (VIII). The yields in all the steps are very good. Instead of ozone, osmium tetroxide-periodate mixture has also been used but the yields have not been very satisfactory.



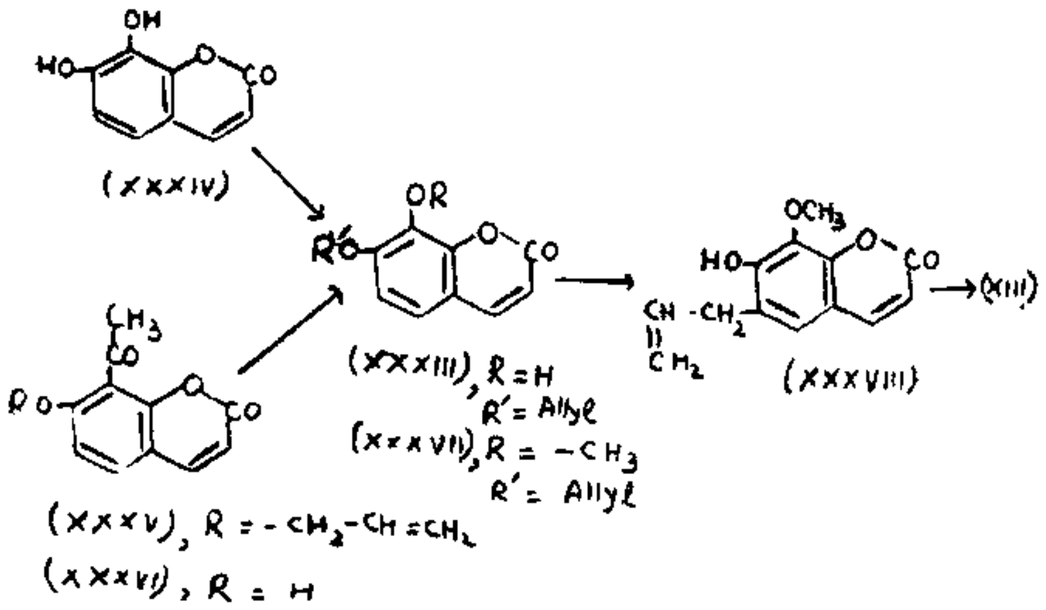
(XXVII), R = R′ = H (XXIX), R = $-CH_3$ (XXV)
(XXVIII), R = H; R′ = Allyl (XXX), R = H
(XXVIII), R = $-CH_3$, R′ = Allyl

Xanthotoxin (*XIII*) is the most active component of the fruits of *Ammi majus*.[10,11] It occurs in many other plant sources and was earlier prepared by two different methods. Spath and Pailer[27] carried out the first synthesis, using 6, 7-dihydroxycoumaran as the intermediate (XXXI). Rodighiero and Antonello[28] used 2, 4-dihydroxy-3-methoxybenzaldehyde (XXXII) and synthesised xanthotoxin by the route as shown below :

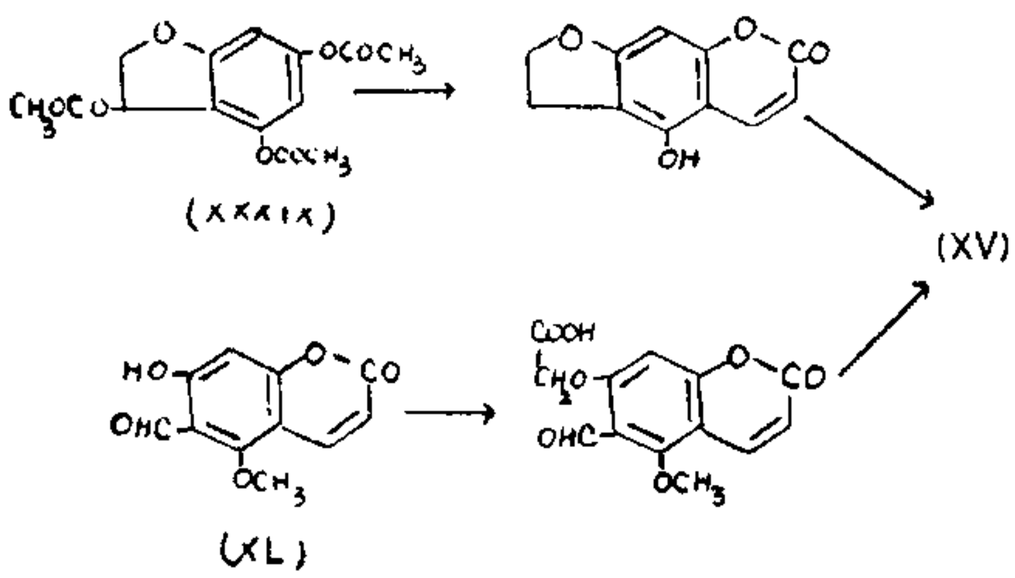


(XXXI) (XIII) (XXXII)

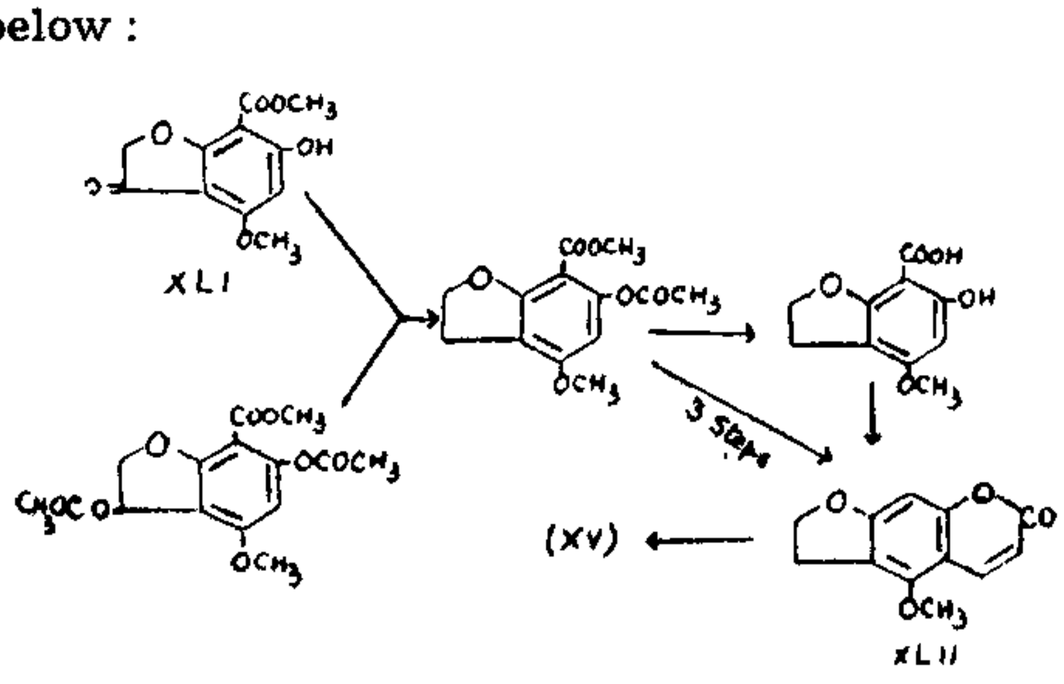
However, the yields were not satisfactory and there was need for a good and convenient synthesis of xanthotoxin. This has recently been achieved and the essential intermediate, 7-allyloxy-8-hydroxycoumarin (XXXIII), has been prepared by the partial allylation of 7, 8-dihydroxycoumarin[29] (XXXIV). It has also been prepared by the Dakin's oxidation of 8-acetyl-7-allyloxycoumarin (XXXV), which was obtained by the allylation of 8-acetyl-7-hydroxycoumarin[30] (XXXVI). 7-Allyloxy-8-hydroxycoumarin (XXXIII) was methylated using dimethyl sulphate and potassium carbonate. The methyl allyl ether (XXXVII) so obtained, was subjected to Claisen migration and the 6-allyl compound (XXXVIII) converted to xanthotoxin employing the method as described in the case of psoralen.



Bergapten (*XV*) is widely distributed in plants. It occurs in bergamot oil and in *Fagara xanthoxyloides* belonging to the family *Rutaceæ*. It was first synthesised by Spath *et al.*[31] starting from 3, 4, 6-triacetoxy coumaran (**XXXIX**) and condensing it with sodioformyl acetate. The resulting product on methylation gave bergapten. Howell and Robertson[32] made it from 6-formyl-7-hydroxy-5-methoxy coumarin (XL) as shown below :



A more convenient synthesis recorded by Caporale[33] involves the protection of the reactive nuclear position with carbomethoxy group and its subsequent removal. The starting material was methyl-4-methoxy-6-hydroxy coumaran-3-one-7-carboxylate (XLI) which was converted to 4', 5'-dihydro-5-methoxy-2', 3' : 7, 6-furanocoumarin (dihydro bergapten) (XLII) by two different methods as indicated below :

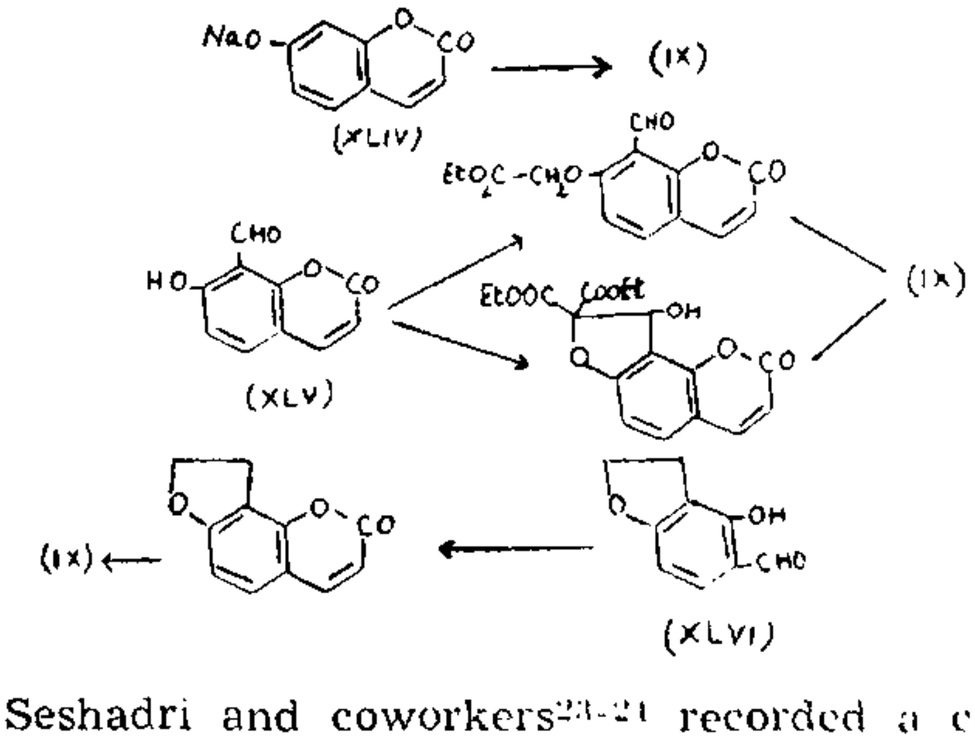


Although this is a good synthesis the number of steps involved and the difficulty in the preparation of the starting material make it inconvenient and so there is need for a good synthesis of bergapten based on the ozonolysis of the corresponding C-allyl compound.

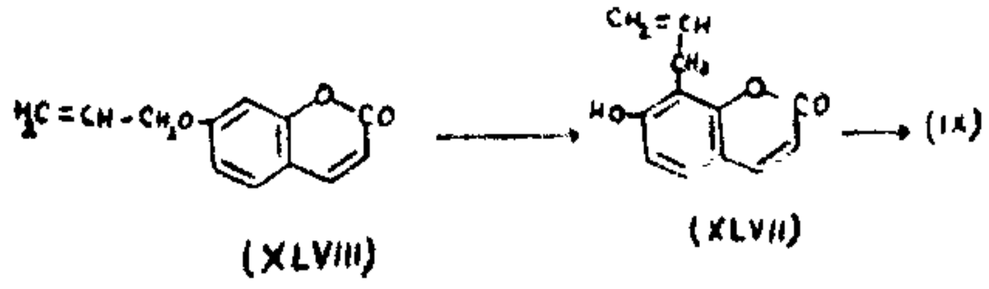
(*b*) *Angular Furanocoumarins*

Angular furanocoumarins have also been found to exibit photodynamic property though not to the same extent as exhibited by the linear isomers. These may be useful for milder effects ; moreover, these are easily prepared as compared to their linear isomers. Musajo and Rodighiero (*loc. cit.*) have shown that angelicin and isobergapten (**XLIII**) are ¼ as active as psoralen. Various approaches to their syntheses are given below.

Angelicin (*IX*) occurs with psoralen, its linear isomer, in the seeds of *Psoralea corylifolia* and in the roots of *Angelica archangelica*. It was first synthesised by Spath and Pailer[34] starting from sodio-umbelliferone (XLIV) and bromoacetal. It has also been prepared from 8-formyl-7-hydroxycoumarin[34] (XLV) as indicated by the route (XLV to IX). Recently, Kawase *et al.*[35] have modified this method using bromomalonic ester instead of bromoacetic ester. Limaye[36] gave a slighily different route, starting from 5-formyl-4-hydroxycoumaran (XLVI). This method gave poor yields, as the preparation of 4-hydroxycoumaran is difficult.

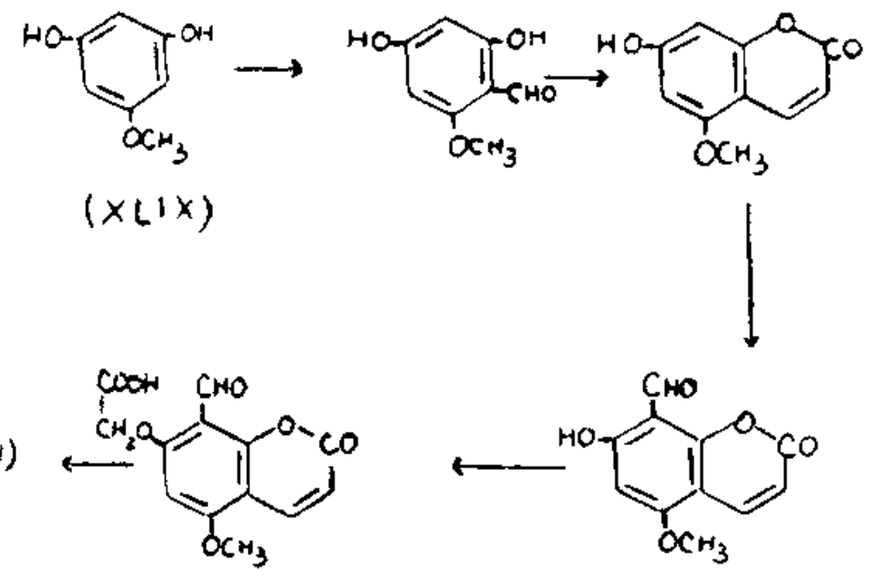


Seshadri and coworkers[23-24] recorded a convenient synthesis of angelicin. 8-Allyl-7-hydroxycoumarin (XLVII), obtained by the Claisen migration of 7-allyloxycoumarin (XLVIII), was subjected to ozonolysis or



osmium tetroxide-periodate oxidation and the intermediate acetaldehyde was cyclised to angelicin in very good yields.

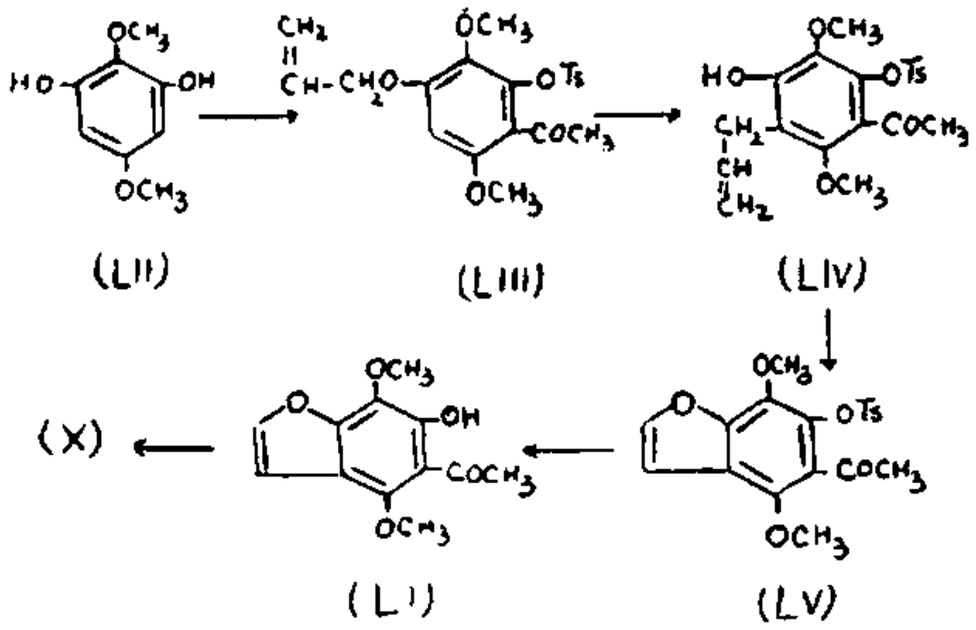
Isobergapten (*XLIII*) occurs in *Pimpinella saxifraga* and was first synthesised by Rodighiero and Antonello[37] starting from phlorogucinol monomethyl ether (XLIX). The various steps involved in the synthesis are indicated below. Since the reported yields are not satisfactory, there is need for a good and convenient synthesis of isobergapten based on the ozonolysis of the appropriate C-allyl compound.



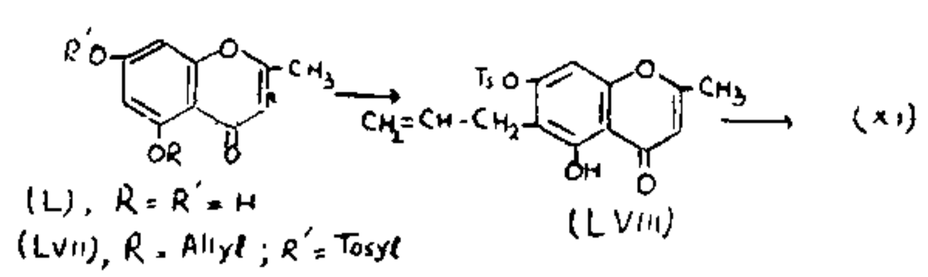
Chromone Derivatives

For a considerable length of time, the seeds of *Ammi visnaga* were claimed to be efficacious in the treatment of leucoderma and this property was attributed to the presence of two furanochromones, kellin and visnagin. It was later shown that the seeds of *Ammi majus*, a closely related plant containing the furanocoumarins, were the more active drugs. Still the furanochromones and furanoflavones seem to have some, though weak, effect on leucoderma and they are sometimes desirable because of their milder action.

Kellin (X) is the chief active component of seeds of *Ammi visnaga* and has been synthesized by a number of methods. The earliest method[38] consisted in the introduction of a furan ring in 2-methyl-5 : 7–dihydroxychromone (L) but it does not always work satisfactorily. A successful synthesis of kellin was carried out by oxidation of visnagin, which had been obtained from 2-methyl-5 : 7–dihydroxy–chromone. This is later discussed under visnagin. The direct methods for the synthesis of kellin, using kellinone (LI) as intermediate are definitely better. Kellinone has been made by a number of methods,[39–41] and the most satisfactory is that of Aneja *et al.*[42] 2, 5-Dimethoxyresorcinol (LII) was converted to 2-tosyloxy–3 : 6-dimethoxy-4–allyloxyacetophenone (LIII), which on Claisen migration yielded the C-allylacetophenone (LIV). Ozonolysis followed by cyclodehydration gave 2-O-tosyl kellinone (LV) which, on hydrolysis, yielded kellinone. This was then converted to kellin by employing the diketone method.



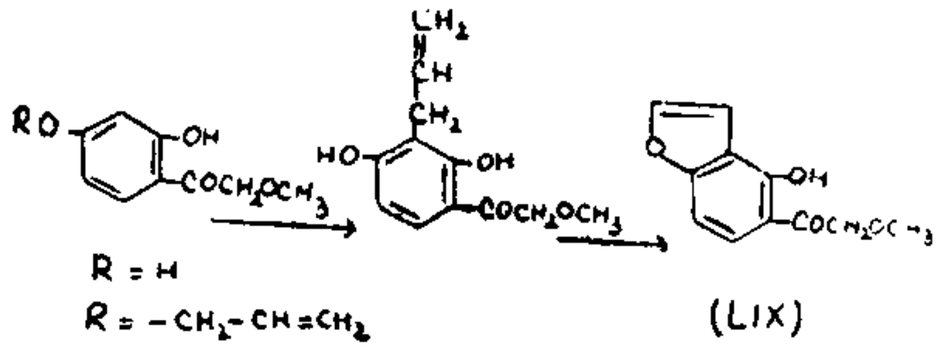
Visnagin (XI) is the second important component of the seeds of *Ammi visnaga* and has been synthesized by a number of methods. The earlier methods[43–45] involved visnaginone as the intermediate but gave poor yields of visnagin because of the possibility of formation of isomeric compounds. Aneja *et al.*[46] developed a synthesis of visnagin, starting from 5 : 7-dihydroxy-2-methyl chromone, which gave an excellent yield. 5-Allyloxy-2–methyl–7-tosyloxychromone (LVII) was prepared from the dihydroxychromone (L) by tosylation, followed by allylation. On Claisen migration it gave 7-tosyloxy-5-hydroxy-6–allyl–2–methyl–chromone (LVIII), which was converted to visnagin by the ozone-phosphoric acid method.



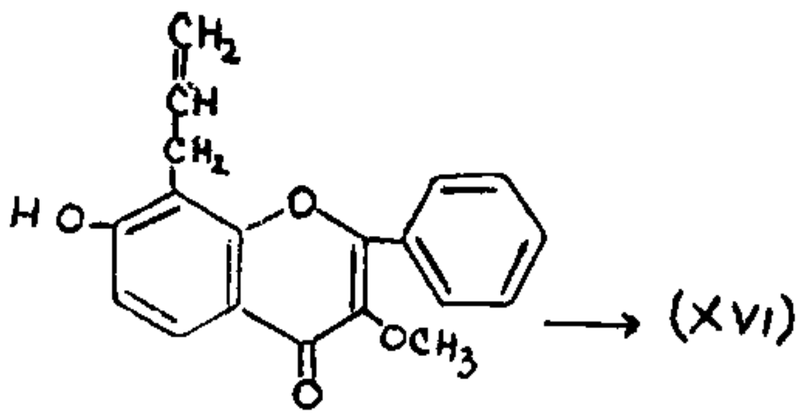
Visnagin can conveniently be converted into kellin. The simplest method[42] consists in demethylating it to norvisnagin followed by persulphate oxidation to nor-kellin and finally methylating to kellin. The yield in this procedure is not good ; it is much improved by the preliminary hydrogenation of the furan ring and final dehydrogenation.

Flavone Group

Karanjin (XVI) is the main component of *Pongamia* seeds and oil. Two main lines for the syntheses have been adopted. The first successful method involved the initial preparation of karanj ketone (LIX), as the main intermediate followed by Allan-Robinson flavone condensation. The earlier procedure adopted by Seshadri and Venkateswarlu[47] involved a large number of steps. Considerable simplification has been achieved in the recent method of Aneja *et al.*[51] who used the following main steps for the preparation of this ketone.



The alternative method of builiding up the furan ring on the flavone unit was first attempted by Rangaswami and Seshadri.[48] There was difficulty at the last decarboxylation stage. Row and Seshadri,[49] however, succeeded in getting a small yield of karanjin. Later Kawase *et al.*[50] obtained a better yield of karanjin by improving the conditions for decarboxylation. This difficulty is completely eliminated and synthesis, simplified by the application of ozonolysis method[51] to 8-allyl-3-methoxy-7-hydroxyflavone (LX), gives good yields of karanjin. Later Raizada *et al.* (*loc. cit.*) used osmium teroxide-periodate mixture for the oxidation of allylic double bond instead of ozone, but the yields are not good.



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