

SYNTHESIS OF CERTAIN SUBSTITUTED PSORALENES  
AND RELATED COMPOUNDS

by

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# SYNTHESIS OF CERTAIN SUBSTITUTED PSORALENES AND RELATED COMPOUNDS

## INTRODUCTION

In recent years the furocoumarin xanthotoxin (9-methoxypsoralene or 9-methoxyfuro(3,2-g)coumarin) has received considerable attention, both in scientific literature and the popular press. Current interest in this compound centers primarily on its ability to accelerate suntanning in humans who have been exposed to ultraviolet light (23, p. 2077-2099). In contrast to other products which are currently used to prevent sunburn, xanthotoxin is administered orally. Other sunburn preventatives are applied topically and their efficacy depends on their physical property of screening out certain frequencies of the solar spectrum. The effectiveness of xanthotoxin, on the other hand, depends on its property of chemically altering the erythermal response to ultraviolet light (17, p. 1; 18, p. 13-15). The specific mechanism for this action is not known, but it may be related to the fact that xanthotoxin is a photosensitizer (6, p. 187-200).

The promotion of rapid tanning to the exclusion of sunburning might seem paradoxical and, indeed, the establishment of dosage level and exposure time have proven

to be delicate problems. A program of too much xanthotoxin and/or too much ultraviolet exposure causes erythma, edema, blistering and pain (23, p. 2077-2079).

What possible toxic effects may result from prolonged use of xanthotoxin have not been established. It was found that rats injected interperitoneally with xanthotoxin showed an increase in incidence of cutaneous carcinomas when exposed to ultraviolet radiation. Conversely, however, oral ingestion of xanthotoxin by rats resulted in a decrease of carcinomas (11, p. 121). According to a recent paper (10, p. 289-295) the longer ultraviolet wavelengths promote a higher incidence of tumors than the shorter wavelengths. Earlier fears that clinical use of xanthotoxin might result in liver damage have been dispelled to some extent, according to a 1958 report by Fitzpatrick (7, p. 1586-1589).

Xanthotoxin is a compound of diverse pharmacological action. Priess (19, p. 94-95) and Späth (28, p. 75-114) have shown it to be toxic to fish. More recently, Schönberg (24, p. 6208) has demonstrated its molluscicidal activity. In the treatment of vitiligo, xanthotoxin gives cosmetically satisfying repigmentation in about one out of seven cases (23, p. 2077-2079). The treatment is tedious and accompanied by many side reactions, but it is currently the best available for

vitiligo.

It may be concluded from the preceding material that while xanthotoxin is highly interesting in a pharmacological sense, it is not wholly satisfactory from a clinical viewpoint.

The fact that the majority of the work done on the photodynamic activity of furocoumarins has centered on xanthotoxin does not necessarily mean this compound is unique in its properties or that it is the best for the purposes under consideration. Probably the principal reason for xanthotoxin's preeminence in this rather new area of scientific investigation is its long history of use for pigmentary disorders by the Egyptians (4, p. 281-291). There has been some work done which indicates xanthotoxin is not, indeed, unique in its photodynamic properties. Musajo (18, p. 13-15), in a comparative study of several furocoumarins, found xanthotoxin second to psoralene in ability to produce pigmentary dermatitis under the influence of ultraviolet light. It is interesting to note that Musajo also showed that the photodynamic activity was clearly associated with the furocoumarin molecule as a whole. The simpler cognates, furan, benzofuran and coumarin were inactive. More recently, Fowlkes (9, p. 571-572) showed that seven of thirteen psoralenes tested in the presence of ultraviolet

light were bactericidal, while all twenty-two variously substituted coumarins tested were inactive.

Though there are numerous other naturally occurring psoralenes that have been reported in the literature, further specific comments on this class of compounds will be limited to psoralene itself. Psoralene was first isolated from a petroleum ether extract of the seeds of Psoralea corylifolia, a plant which thrives throughout India (15, p. 41-46). The oil from these seeds had long been used as a treatment of skin diseases such as leucodermia (15, p. 41-46). Psoralene was first synthesized by Späth (27, p. 1087-1090) in 1936 and has since been synthesized by two essentially different routes (8, p. 2254-2260 and 14, p. 1514-1518) including one to be reported in this paper.

Xanthotoxin was first isolated by Priess (19, p. 94-95), in 1911, from an alcoholic extract of Fagara zanthoxyloides Lam. It was soon characterized by Thoms (29, p. 3325-3332), but it was not until 1936 that it was first synthesized by Späth (30, p. 767-770); its synthesis was accomplished by a different route by Rodighiero in 1956 (22, p. 960-967). More recently, xanthotoxin has been obtained from a petroleum ether extract of the powdered fruits of Ammi majus L. (25, p. 481-482) and from the berries of Luvagno scandens (1,

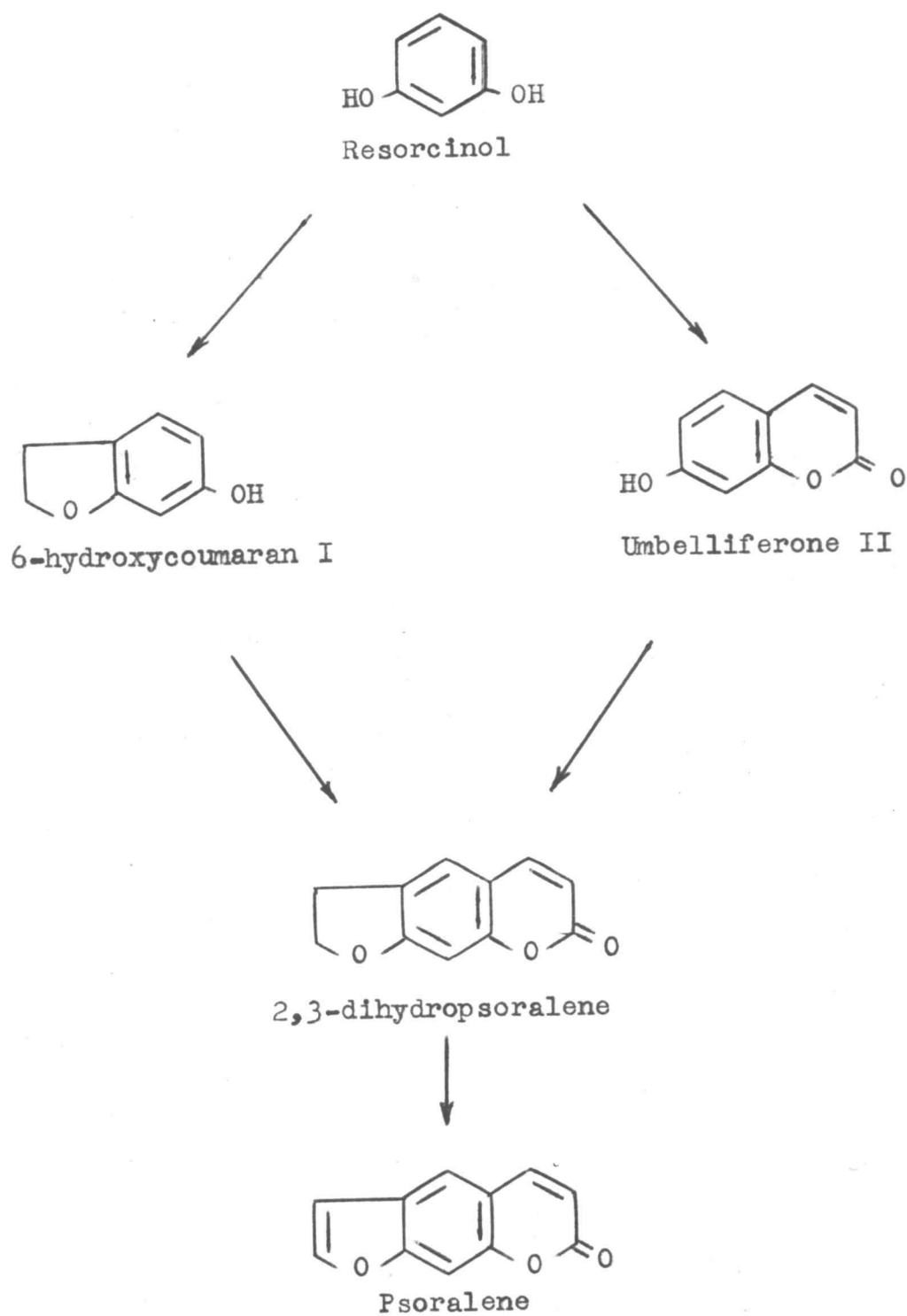
p. 181-186).

One of the reasons for undertaking the work presented in this paper was that while xanthotoxin possessed some highly desirable properties it also had some undesirable features. The limitations of the compound pointed to the need for new psoralene derivatives for testing purposes. Another objective was the development of a new synthetic route to the psoralenes, since the existing procedures were lengthy and/or resulted in poor yield.

The starting material for the synthesis of a psoralene is resorcinol or a resorcinol derivative substituted in the 2- or 5-positions. The synthesis can be accomplished by first completing the five-membered furan ring, thus yielding a 6-hydroxycoumaran (2,3-dihydro-6-hydroxybenzofuran I) or, alternatively, a Pechmann reaction can be employed to yield a 7-hydroxycoumarin (an umbelliferone II). Thus, there is the possibility of using either of the two bicyclic ring systems, coumaran or coumarin, as the starting material for the synthesis of psoralenes (fig. 1).

Späth, in a one step operation using 6-hydroxycoumaran together with malic acid in a sulfuric acid medium, succeeded in preparing 2,3-dihydropsoalene(IV) from which psoralene was obtained by a dehydrogenation

FIGURE 1





procedure (27, p. 1087-1090). Later, Horning and Reisner devised a superior synthesis of the key intermediate, 6-hydroxycoumaran (13, p. 3619-3620), although their route to psoralene was essentially the same as that used by Späth. Horning and Reisner found that 6-acetoxycoumaran, from which their 6-hydroxycoumaran was prepared, was a suitable intermediate for the synthesis of 5-substituted-2,3-dihydropсоралenes; by using a variety of  $\beta$ -ketoesters in this Pechmann type condensation, these workers obtained a series of 5-substituted-2,3-dihydropсоралenes. In all these condensations the reactions were carried out in 75% sulfuric acid. All dehydrogenations were effected by refluxing the dihydro derivatives in phenyl ether in the presence of palladized charcoal.

A second route, also employing a coumaran for the synthesis of psoralenes, was reported concurrently by Robinson and Horning and Reisner. The starting compound in this new procedure was 6-hydroxycoumaran(I). This intermediate was formylated in the 5-position by means of a Gattermann reaction. The formyl derivative (V) was, in turn, condensed with cyanoacetic acid (8, p. 2254-2260) or malonic ester (14, p. 1514-1518), thus yielding a psoralene nucleus. The resulting 6-carboxy-2,3-dihydropсоралene(VI) was then decarboxylated and dehydrogenated to yield psoralene itself.

Rây (20, p. 813-816), in attacking the problem of furocoumarin synthesis from the coumarin moiety of the psoralene molecule, has synthesized 3-methylpsoralene(VII). In this procedure, 7-acetonyloxy coumarin(VIII) was prepared by reacting umbelliferone with chloroacetone. Cyclization of this intermediate to 3-methylpsoralene was accomplished in an ethanolic medium using sodium ethoxide as the condensing agent. In this respect the ring closure was markedly different from the usual pattern.

Another illustration of the approach from a coumarin to a psoralene is Rodighiero's synthesis of xanthotoxin(IX). This procedure made use of 7-hydroxy-8-methoxycoumarin, which was formylated with hexamine to yield the 6-formyl derivative(X). The furan ring was then completed using bromoethyl acetate to effect closure (25, p. 960-967).

The four synthetic routes to psoralenes described above, of which two are based on the use of an umbelliferone and two on the use of 6-hydroxycoumaran, are illustrated in figures 2 and 3.

One other reaction is pertinent to this discussion. Using xylene as the solvent, Späth reacted bromoacetal and the sodium salt of umbelliferone in a sealed tube at 170°C. The product was not psoralene, but its angular



FIGURE 2

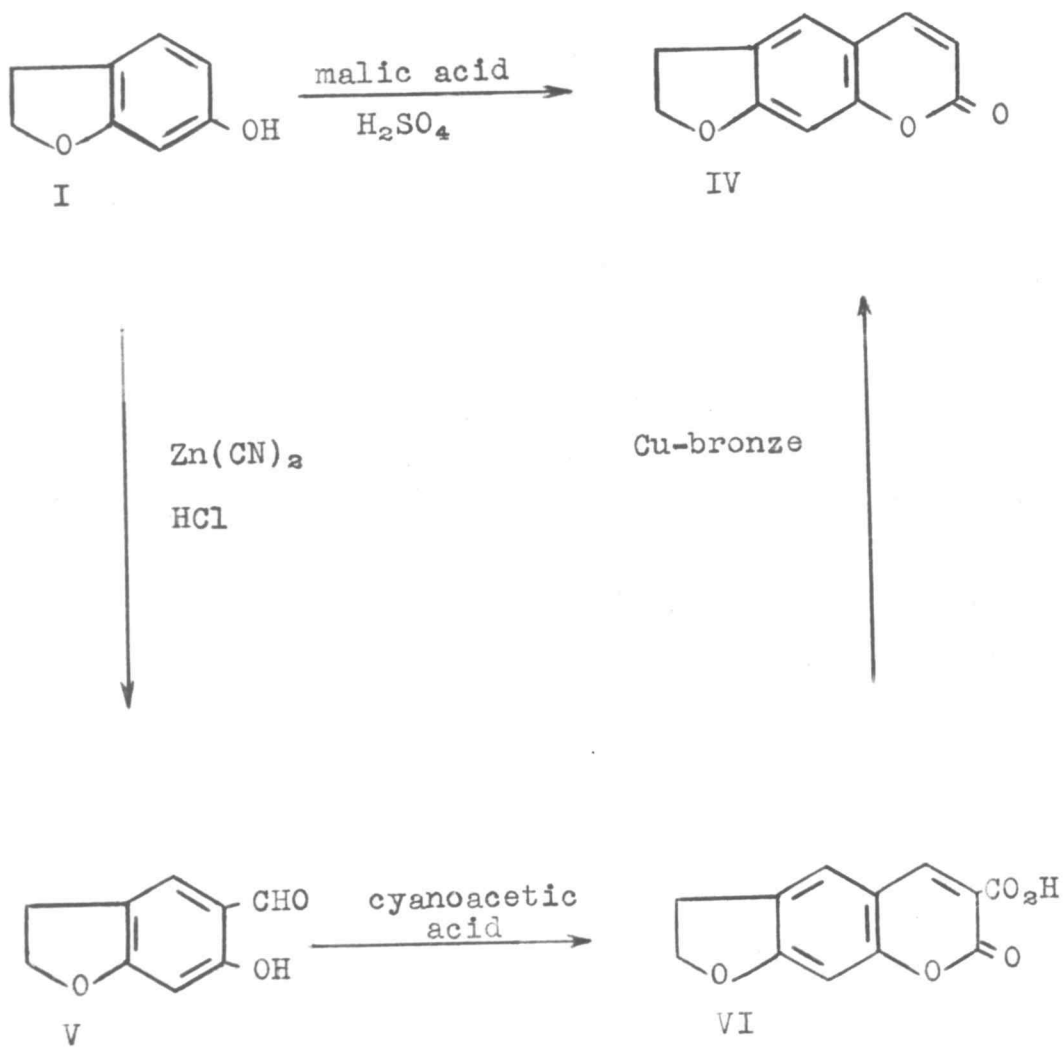
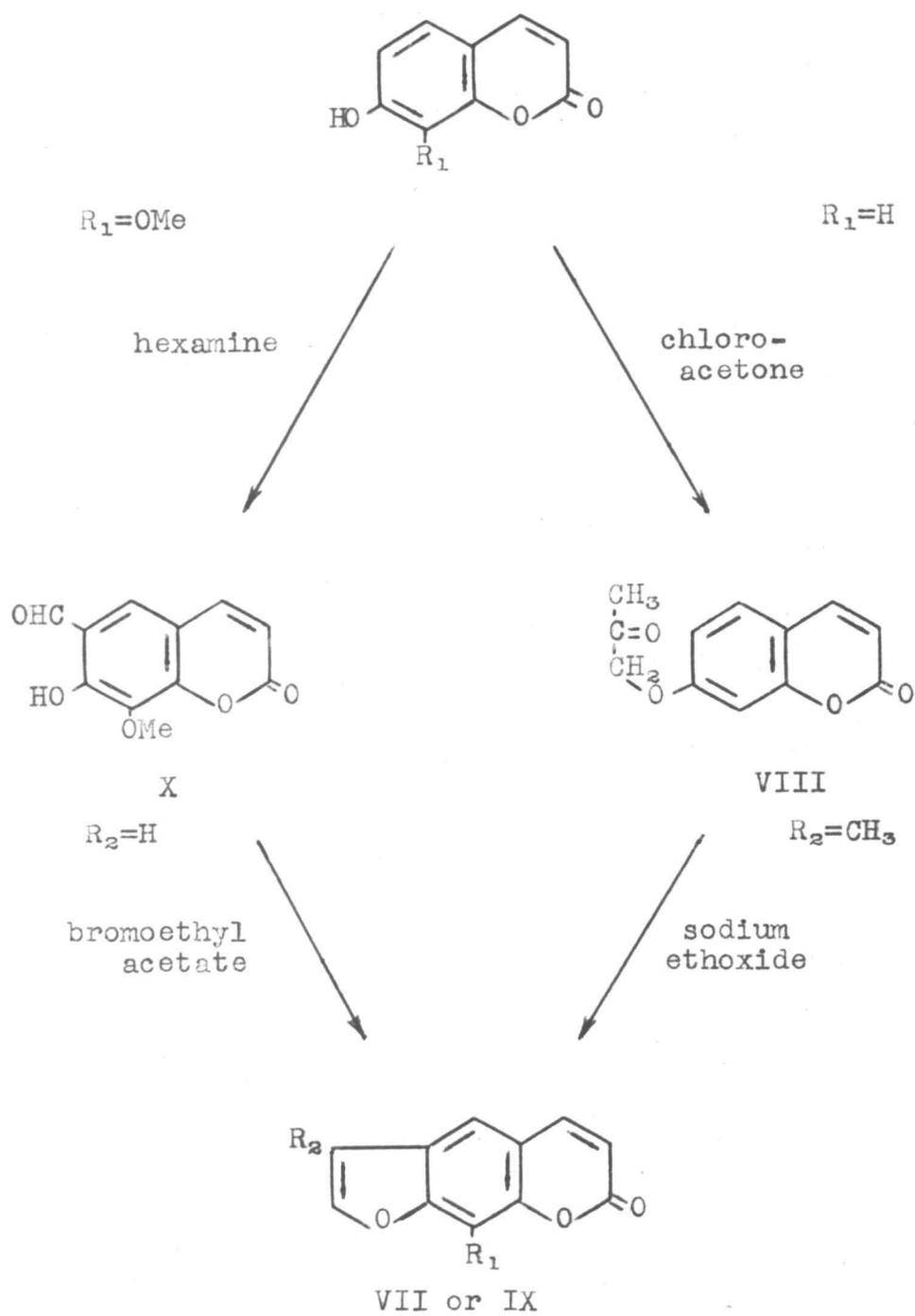


FIGURE 3



isomer, angelicin (furo(2,3-h)coumarin). The yield, however, was very small; two grams of the sodium salt of umbelliferone gave only eighteen milligrams of angelicin (29, p. 1212-1213).

## DISCUSSION

Horning and Reisner have reported the synthesis of four alkyl or aryl 5-substituted psoralenes by a Pechmann type synthesis (14, p. 1514-1518). The method these workers employed was to condense 6-acetoxycoumaran with a  $\beta$ -ketoester in the presence of 75% sulfuric acid. The resulting products, 5-substituted 2,3-dihydro-psoralenes, were dehydrogenated with a palladium on charcoal catalyst to give the 5-substituted psoralenes. The procedure appeared to be of such generality that it could be adapted to other  $\beta$ -ketoesters, and a program of making a number of 5-substituted and 5,6-disubstituted psoralenes was initiated.

A series of 6-alkyl-2,3-dihydro-5-methylpsoralenes was prepared by condensing the appropriate  $\alpha$ -alkyl  $\beta$ -ketoesters with 6-acetoxycoumaran. The compounds prepared by this procedure were the 5,6-dimethyl-, 6-ethyl-5-methyl-, 6-isopropyl-5-methyl- and 6-myristyl-5-methyl-derivatives of 2,3-dihydro-psoralene. With the exception of 2,3-dihydro-5-methyl-6-myristylpsoralene, all of these compounds were dehydrogenated by refluxing in phenyl ether in the presence of 10% palladium on charcoal. Repeated and prolonged attempts to remove hydrogen from the myristyl derivative invariably resulted in the recovery

of the unchanged starting material.

The synthesis of 2,3-dihydro-5-methyl-6-myristyl-psoralene required the preparation of ethyl  $\alpha$ -myristyl-acetoacetate. Since no directions could be found for the preparation of this compound, a procedure based on the general method for making  $\alpha$ -alkyl substituted ethyl acetoacetates was employed (12, p. 248-249). These directions proved to be quite satisfactory.

In an attempt to prepare 5-carboxy-2,3-dihydro-psoralene(XI), the sodium salt of diethyl oxalacetate was reacted with 6-acetoxycoumaran in the presence of 75% sulfuric acid, following the usual procedure. For some unknown reason, all initial attempts were unsuccessful; a tarry product always resulted, from which nothing could be isolated. However, as the author became more experienced with the reaction, conditions were devised by which the condensation was successfully completed in a 75% sulfuric acid medium.

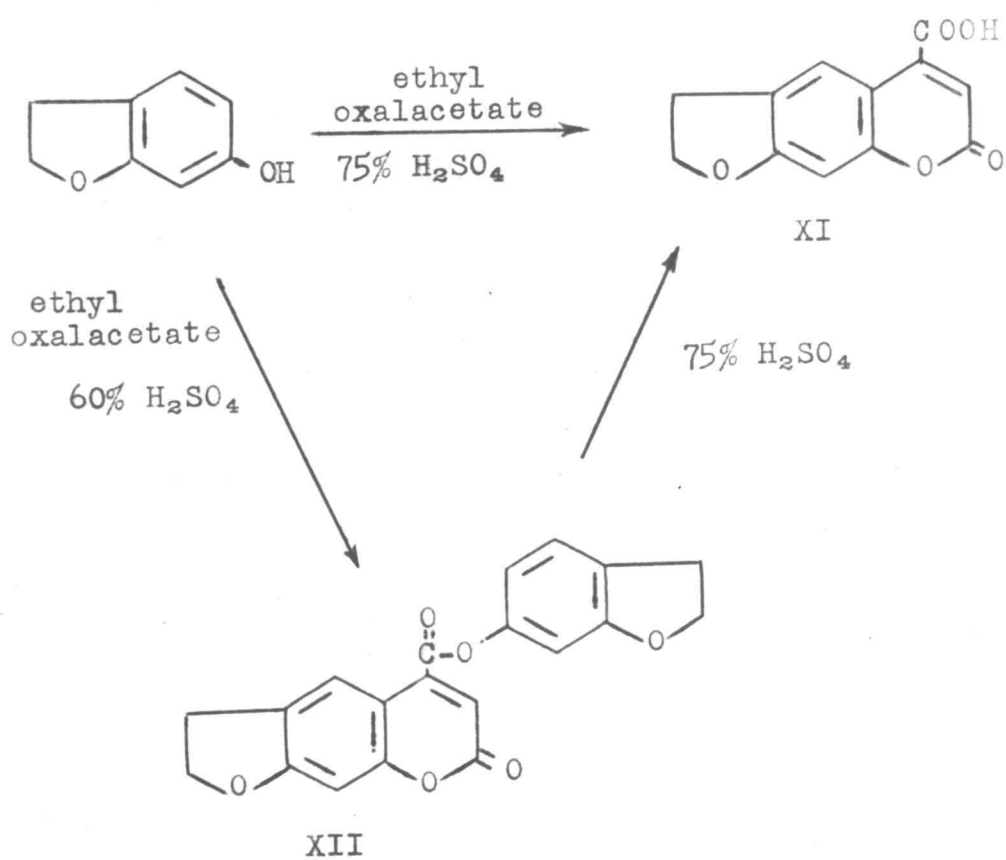
In the meantime, because of these initial failures and in view of the tarry nature of the reaction product, the concentration of the sulfuric acid in the reaction medium had been reduced to 60% in several experiments. The use of the more aqueous medium yielded a product having a sharp melting point which was not the desired

compound. Carbon and hydrogen analysis indicated the empirical formula to be  $C_{10}H_7O_3$ . A molecular weight determination (Rast) showed the molecular formula to be  $C_{20}H_{14}O_6$ .

An examination of the infrared spectrum of this compound revealed the presence of two carbonyl groups and the absence of either hydroxyl or carboxyl substituents. Treatment of this product by the usual dehydrogenation procedures yielded a dehydrogenated product with a molecular formula  $C_{20}H_{10}O_6$ , which indicated that the compound may have possessed two dihydrofuran ring systems. When this product was, in turn, treated in 75% sulfuric acid medium the desired compound, 5-carboxy-2,3-dihydropsoralene, was isolated from the reaction mixture.

On the basis of this data it was concluded that the sequence of reactions responsible for these changes was that shown in figure 4. However, experiments designed to confirm the hypothesis that  $C_{20}H_{14}O_6$  was the ester 6-coumaranyl 2,3-dihydropsoralene-5-carboxylate(XII) failed. Repeated attempts to saponify the compound under various conditions of basic hydrolysis were unsuccessful. This resistance to hydrolysis is surprising and although it may be due to steric factors, it leaves the question of structure somewhat unsettled.

FIGURE 4



Horning and Reisner have obtained psoralene by a simultaneous decarboxylation and dehydrogenation of 6-carboxy-2,3-dihydropsoalene (14, p. 1514-1518). Similar treatment of the 5-carboxy-2,3-dihydropsoalene prepared in this laboratory yielded the expected psoralene.

Since condensation of ethyl oxalacetate with 6-acetoxycoumaran had yielded 5-carboxy-2,3-dihydro-psoralene, which by dehydrogenation and decarboxylation procedures had, in turn, yielded psoralene, the possibility of preparing the 6-methyl homolog by the use of ethyl oxalpropionate was at once apparent.

Identical conditions of condensation, namely a 60% sulfuric acid medium, yielded a product similar to that obtained with oxalacetate, with an apparent molecular weight of 354 (Rast) and a molecular formula of  $C_{21}H_{12}O_6$  (the calculated molecular weight is 364). This compound also lost four hydrogen atoms per mole in dehydrogenation operations. Its infrared spectrum was very similar to the  $C_{20}H_{14}O_6$  compound previously obtained and indicated the presence of two carbonyl groups and the absence of either carboxyl or hydroxyl substituents.

When this ester was treated with 75% sulfuric acid, as in the case of  $C_{20}H_{14}O_6$ , no cleavage was noted. Thus this ester, postulated to be 6-coumaranyl 2,3-dihydro-6-methyl-5-carboxylate, appears to be stable to both acid



and basic hydrolysis.

Attempts to produce 5-carboxy-2,3-dihydro-6-methyl-psoralene by direct condensation using 75% sulfuric acid as the condensing agent resulted not in the free acid, but instead the same product obtained when using 60% sulfuric acid.<sup>1</sup>

5-Hydroxypsoralene was one of the psoralenes desired for screening purposes by this laboratory. Horning and Reisner (14, p. 1514-1518) had succeeded in preparing the 2,3-dihydro-5-hydroxypsoralene but were unable to dehydrogenate the compound. For this reason 2,3-dihydro-5-hydroxypsoralene was acylated and then subjected to dehydrogenation operations. This 5-acetoxy derivative, however, was stable at the reflux temperatures of phenyl ether and the compound was recovered unchanged from the reaction mixture. Conversion of the 2,3-dihydro-5-hydroxypsoralene to the 5-methoxy derivative yielded a compound which readily responded to dehydrogenation, yielding a compound isomeric to xanthotoxin.

The syntheses of the compounds described in the preceding section require either 6-acetoxycoumaran or 6-hydroxycoumaran as intermediates. Preparations of

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<sup>1</sup>The free acid did, apparently, result from one run. The compound isolated had a melting point of over 300°C. and gave the correct analysis for the free acid. The reaction could not be repeated.

these materials require three and four steps, respectively, beginning with the starting material, resorcinol. The Pechmann type reaction used to form the 2,3-dihydro-psoralenes is not a clean reaction. The yields are poor, and often two or three crystallizations using large amounts of decolorizing charcoal are necessary. Finally, the product must be dehydrogenated; thus, from five to seven steps are required to obtain the psoralenes described in the preceding section. Because of the poor yields, together with size limitations of laboratory reactions, considerable work is required, in practice, to obtain as much as a gram of any given psoralene.

Of the three remaining synthetic routes previously discussed (figures 2 and 3) the two involving formylation (of a hydroxycoumaran in one case, and an umbelliferone in the other) appear as lengthy and inefficient as the route employing the  $\beta$ -ketoester condensation. On the other hand, the fourth procedure, as reported by Rây (20, p. 813-816) requires only three steps from resorcinol to a 3-substituted psoralene. This method is also attractive in that an umbelliferone is an intermediate rather than a 6-hydroxycoumaran. Umbelliferones can be synthesized quite simply and in some variety (26, p. 1-58). The second step of Rây's procedure is based on an ether formation from an  $\alpha$ -haloketone and an umbelliferone. The

keto derivative is next submitted to ring closure under the influence of sodium ethoxide. The formation of the keto derivative proceeds smoothly but, that the ring closure step is satisfactory could not be confirmed in this laboratory.<sup>1</sup>

Even if the ring closure were to proceed in good yield, Rây's procedure is, as far as known, restrictive, in that its application results in a psoralene substituted in the 3-position. To eliminate this restriction it would be necessary to utilize a 7-(2-oxoethoxy)-coumarin. It would appear that this intermediate might be synthesized merely by reacting chloroacetaldehyde with an umbelliferone in the presence of sodium ethoxide. An attempt by the author to synthesize 7-(2-oxoethoxy)-4-methylcoumarin in this way was unsuccessful and resulted in the recovery of unchanged 4-methylumbelliferone.

The synthesis of 7-(2-oxoethoxy)-4-methylcoumarin was accomplished, however, by two methods; both started with 7-allyloxy-4-methylcoumarin. The first method was based on a permanganate oxidation of the allyl double bond to yield the diol, 7-(2,3-dihydroxypropoxy)-4-methylcoumarin. The diol, in turn, was cleaved with periodic

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<sup>1</sup>Rây does not report the yields for this step. Three attempts were made in this laboratory to synthesize 3,5-dimethylpsoralene as reported by Rây. The first two attempts were complete failures. The third try resulted in a 4% yield of product.

acid to yield the desired aldehyde. The second method was based on the ozonolysis of the allyl derivative to yield the desired aldehyde. The ozonolysis method was also used to prepare 7-(2-oxoethoxy)-coumarin from the appropriate allyl derivative.

Following the successful preparation of the intermediates, the sodium ethoxide ring closure on 7-(2-oxoethoxy)-4-methylcoumarin was attempted. However, base catalyzed ring closures were unsuccessful. Invariably the ether linkage was cleaved and 4-methylumbelliferone was recovered from the reaction.

The failure of the base catalyzed ring closure led to the use of several different acid catalysts under varying conditions. Among the catalysts tried were aluminum chloride, zinc chloride, boron trifluoride, sulfuric acid, polyphosphoric acid, phosphorous pentoxide, phosphorous oxychloride, 48% hydrobromic acid and hydrobromic acid with acetic acid. Experiments with these catalysts led to either: 1) recovery of starting material; 2) an uncharacterizable tar; or 3) ether cleavage, with the recovery of 4-methylumbelliferone. An attempted cyclization using acetic anhydride with 48% hydrobromic acid resulted in formation of the acylal derivative.

In anticipation of successful ring closure, 7,8-bis-(2-oxoethoxy)-4-methylcoumarin had also been synthesized. This dialdehyde was obtained by ozonolysis of the corresponding diallyl compound. The diallyl derivative was prepared from allyl bromide and the previously known 7,8-dihydroxy-4-methylcoumarin. In view of the failure of the cyclization experiments, no extensive attempts to effect ring closure were made with this intermediate.

Coumaran has been prepared from  $\beta$ -bromoethyl phenyl ether using zinc chloride as a catalyst (21, p. 665-670). However, 7-(2-bromoethoxy)-4-methylcoumarin synthesized in this laboratory, could not be cyclized to the corresponding dihydrofurocoumarin. Both zinc chloride and aluminum chloride brought about ether cleavage rather than the desired cyclization. Milder conditions, on the other hand, resulted in the recovery of unchanged starting material.

A German patent discloses the synthesis of 2-methylcoumaran from O-allylphenol by heating at 220°C. with pyridine hydrochloride (5, p. 1214). 7-Allyloxy-4-methylcoumarin, when subjected to the same treatment, undergoes ether cleavage, 4-methylumbelliferone being recovered.

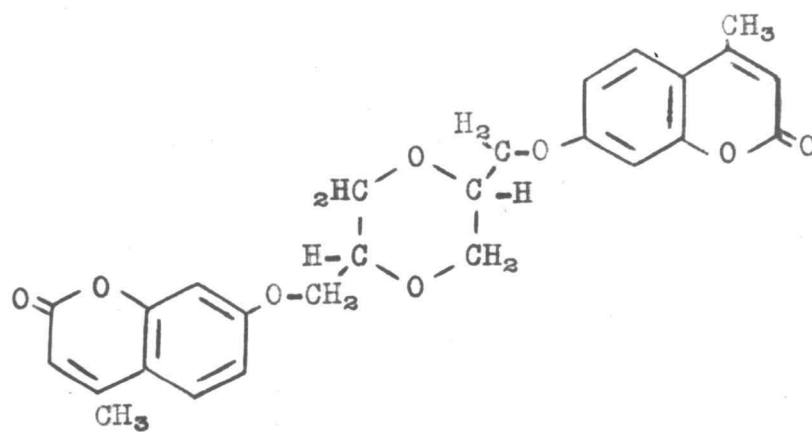
The synthesis of 7-(2,3-dihydroxypropoxy)-4-methylumbelliferone, described in an earlier paragraph, by a

permanganate oxidation of 7-allyloxy-4-methylcoumarin, is cumbersome in that it requires large volumes of oxidizing solution. It appeared that a better route to the desired diol might be to form 7-(2,3-epoxypropoxy)-4-methylcoumarin and then open the epoxide ring to yield the diol.

Although the reaction between 4-methylumbelliferone and epichlorohydrin appeared to proceed smoothly enough, the resultant product did not have any of the properties of the epoxide compound. It could not be cleaved by refluxing in 20% hydrochloric acid solution. This compound's resistance to ring opening by acid made it apparent that the epoxide group was not present. Carbon and hydrogen analysis indicated that the empirical formula was  $C_{13}H_{12}O_4$  (correct for the desired epoxy compound); however, a molecular weight determination (Rast) gave a value of 480. From this evidence it appeared probable that the compound isolated was a dimer of the desired epoxy compound (the calculated molecular weight of the dimer,  $C_{26}H_{12}O_8$ , is 464). There is evidence that dimers are, indeed, sometimes formed from ethoxides. Cohen reported that 2,5-dimethyl-2,5-diphenyl-p-dioxane resulted from acid treatment of methylphenylethylene oxide (2, p. 898), and Winstein suggested that 1-epoxyethyl-4-methoxynaphthalene dimerized to some extent to a

2,5-substituted p-dioxane during a vacuum distillation (32, p. 157-162). Thus a substituted dioxane (fig. 5, XIII) is a plausible structure for the dimer,  $C_{26}H_{12}O_8$ , although this configuration has not been definitely established.

FIGURE 5



XIII



## EXPERIMENTAL

2,3-Dihydro-5,6-dimethylpsoralene. A mixture containing 6-acetoxycoumaran (1.78 g.) and ethyl  $\alpha$ -methylacetoacetate (1.42 g.) was placed on a steam bath; 10 ml. of 75% sulfuric acid was added with stirring over a 10-minute period. Heating and stirring were continued for an hour; the reaction mixture was then cooled and poured onto ice. The mixture was placed overnight in a refrigerator and then filtered and washed with cold water. The crude product was decolorized with charcoal and recrystallized, first from ethyl acetate and then from ethanol; yield 0.45 g. (21%), m.p. 186.5-187.5°.

Anal. Calcd. for  $C_{13}H_{12}O_3$ : C, 72.2; H, 5.56.  
Found: C, 72.2; H, 5.60.

2,3-Dihydro-6-ethyl-5-methylpsoralene.

6-Acetoxycoumaran (1.78 g.) and ethyl  $\alpha$ -ethylacetoacetate (1.58 g.) were treated in the same manner as in the above experiment. The crude product was decolorized with charcoal and recrystallized twice with ethanol; yield 0.80 g. (35%), m.p. 143-144°.

Anal. Calcd. for  $C_{14}H_{14}O_3$ : C, 73.0; H, 6.18.  
Found: C, 72.5; H, 6.12.

2,3-Dihydro-6-isopropyl-5-methylpsoralene.

6-Acetoxy coumaran (1.76 g.) and ethyl  $\alpha$ -isopropylacetoacetate (1.72 g.) were treated in an identical manner to that employed for the preparation of 2,3-dihydro-6-ethyl-5-methylpsoralene. The yield was 0.60 g. (25%), m.p. 183-185°.

Anal. Calcd. for  $C_{15}H_{16}O_3$ : C, 73.7; H, 6.56.

Found: C, 73.6; H, 6.84.

2,3-Dihydro-5-methyl-6-myristylpsoralene. Eight

ml. of 75% sulfuric acid was added dropwise to a stirred mixture of 6-acetoxy coumaran (0.89 g.) and ethyl  $\alpha$ -myristylacetoacetate (1.63 g.). The reaction was started at room temperature and gradually brought to 65°. After 2 hours the mixture was cooled and poured onto ice. The precipitate was collected, decolorized with charcoal and recrystallized twice from dilute ethanol; yield 0.76 g. (38%), m.p. 96-97°.

Anal. Calcd. for  $C_{26}H_{38}O_3$ : C, 78.4; H, 9.55.

Found: C, 77.9; H, 9.54.

Dehydrogenation of the 5,6-dialkyl-2,3-dihydro-psoralenes. The following procedure was used to dehydrogenate the 5,6-dialkyl-2,3-dihydro-psoralenes (see Table 1).

Table 1

## 5,6-Dialkylpsoralenes

Psoralenes	Yield %	M.P.	Molecular Formula	Carbon		Hydrogen	
				Calcd.	Found	Calcd.	Found
5,6-Dimethyl-	45	235-236°	$C_{13}H_{10}O_3$	72.9	72.9	4.61	4.61
6-Ethyl-5-methyl-	55	179-180°	$C_{14}H_{12}O_3$	73.7	73.4	5.26	5.40
6-Isopropyl-5-methyl-	44	145-147°	$C_{15}H_{14}O_3$	74.3	74.0	5.80	5.89

One gram of the compound to be dehydrogenated was added, together with 10% palladium on charcoal (0.5 g.), to 15 ml. of phenyl ether, and the mixture was then refluxed for 8 hours. The hot solution was filtered to remove the catalyst, which was washed with 5 ml. of hot phenyl ether. The phenyl ether was removed from the product by a steam distillation. The non-volatile residue was collected, decolorized with charcoal and crystallized from ethanol.

Ethyl  $\alpha$ -myristylacetoacetate. Ethyl acetoacetate (6.5 g.), together with 100 ml. of absolute ethanol and 1.15 g. of sodium (converted to sodium ethoxide) were placed in a three-necked flask, equipped with stirrer, reflux condensor and separatory funnel. This solution was stirred, brought to a boil and n-myristyl bromide (13.9 g.) was added over a two-hour period. The reaction was continued until the solution was neutral to litmus. When the reaction was complete, the cooled solution was decanted from the sodium bromide. The alcohol was removed by a simple distillation and the product was then distilled under reduced pressure. The fraction collected boiled at 180-185° at about 0.5 mm.; yield 12.9 g. (79%),  $n_D^{23}$  1.4510.

Anal. Calcd. for  $C_{20}H_{38}O_3$ : C, 73.6; H, 11.65.  
Found: C, 73.5; H, 11.41.

2,3-Dihydro-5-methoxypsoralene. One and a half grams of 2,3-dihydro-5-hydroxypsoralene (14, p. 1514-1518) in 50 ml. of acetone was refluxed with potassium carbonate (3.75 g.) and dimethyl sulfate (1.5 ml.) for 18 hours. The mixture was poured into 200 ml. of water, cooled and the product collected and recrystallized from ethanol; yield 0.9 g. (56%), m.p. 209-210°.

Anal. Calcd. for  $C_{12}H_{10}O_4$ : C, 66.1; H, 4.59.  
Found: C, 66.0; H, 4.78.

5-Methoxypsoralene. 2,3-Dihydro-5-methoxypsoralene (0.63 g.) was dehydrogenated by the general procedure given. The crude product was recrystallized from ethanol; yield 0.41 g. (65%), m.p. 216-217°.

Anal. Calcd. for  $C_{12}H_8O_4$ : C, 66.7; H, 3.71.  
Found: C, 66.5; H, 3.91.

2,3-Dihydro-6-acetoxypsoralene. 2,3-Dihydro-5-hydroxypsoralene (0.53 g.) was refluxed with 10 ml. acetic anhydride and 0.5 ml. pyridine for 3 hours, after which the solution was poured into water. The product was collected and recrystallized from ethanol; yield 0.35 g. (55%), m.p. 225-227°.

Anal. Calcd. for  $C_{13}H_{10}O_5$ : C, 63.4; H, 4.07.

Found: C, 63.4; H, 4.27.

6-Coumaranyl 2,3-dihydropsoralene-5-carboxylate (?).

6-Acetoxy coumaran (5.24 g.) was melted in a flask on a steam bath. The sodium salt of diethyl oxalacetate (6.9 g.) was added and the mixture stirred into a paste. The heating was then stopped and 30 ml. of 60% sulfuric acid was added over a 30-minute period. Stirring was continued for another 30 minutes and the mixture then replaced on a steam bath for an additional 15 minutes. The reddish mixture was cooled, poured onto ice and left in a refrigerator overnight. The product was then collected and washed with cold water. The dry, crude product was improved by washing with very small portions of ethyl ether. Decolorization with charcoal and recrystallization from ethanol gave 2.95 g. (56%) of pale yellow needles, m.p. 209-210°.

Anal. Calcd. for  $C_{20}H_{14}O_6$ : C, 68.6; H, 4.00.

Found: C, 68.4; H, 4.23.

2,3-Dihydro-5-carboxypsoralene. 6-Acetoxy coumaran

(3.56 g.) was melted and stirred into a paste with the sodium salt of diethyl oxalacetate (4.60 g.). Twenty ml. of 75% sulfuric acid was added over a 30-minute period.

The temperature was then raised to 80° and the stirred mixture maintained at this temperature for an additional 30 minutes; it was then cooled, poured onto ice and set in a refrigerator overnight. The product was filtered, washed with water and dissolved in 100 ml. of hot 1% sodium hydroxide solution. The basic solution was filtered and the product precipitated from the filtrate with dilute hydrochloric acid. The product was collected and recrystallized from ethanol; yield 0.71 g. (20%), m.p. 254-256°.

Anal. Calcd. for  $C_{12}H_8O_5$ : C, 62.1; H, 3.45.  
Found: C, 62.2; H, 3.73.

Psoralene. 2,3-Dihydro-5-carboxypsoralene (0.5 g.) and 0.25 g. of 10% palladium on charcoal were refluxed in 10 ml. of phenyl ether for 5 hours. The mixture was filtered while hot to remove the catalyst, which was washed with 5 ml. of hot phenyl ether. The solution was added to 200 ml. petroleum ether (b.p. 60-71°) and cooled at -10° overnight. The amorphous product was collected and recrystallized from ethanol; yield 0.18 g. (85%), m.p. 155-160°. Sublimation at 150° and 12 mm. gave a material melting at 160-161°. A mixed melting point with an authentic sample of psoralene gave no depression of the melting point.

Anal. Calcd. for  $C_{11}H_6O_3$ : C, 71.0; H, 3.23.

Found: C, 70.6; H, 3.42.

The infrared spectrum was identical to that of an authentic sample of psoralene.

6-Coumaranyl 2,3-dihydro-6-methyl-5-carboxylate(?).

Ten ml. of 60% sulfuric acid was added, with stirring, to a mixture of 6-acetoxycoumaran (1.78 g.) and diethyl oxalpropionate (4.64 g.) over a 25-minute period. The temperature was raised to  $85^\circ$  and maintained there while stirring was continued for another 25 minutes. The mixture was then cooled and poured onto ice. The product was collected, washed with water and twice decolorized with charcoal during ethanol recrystallization; yield 0.6 g. (33%), m.p.  $248-250^\circ$ .

Anal. Calcd. for  $C_{21}H_{16}O_6$ : C, 69.2; H, 4.39.

Found: C, 69.4; H, 4.52.

5-Carboxy-2,3-dihydropsoralene. 6-Coumaranyl

2,3-dihydropsoralene-5-carboxylate(?) (0.5 g.) was added to 75% sulfuric acid (3 ml.) and the mixture was stirred for 25 minutes at room temperature. The temperature was then raised to  $80^\circ$  and maintained at this temperature while stirring was continued an additional 25 minutes. The reaction mixture was cooled and poured onto ice.



The product was filtered and washed with cold water. Recrystallization from dilute ethanol yielded 110 mg. (15%), m.p. 253-255°.

Anal. Calcd. for  $C_{12}H_8O_5$ : C, 62.1; H, 3.45.  
Found: C, 62.5; H, 3.69.

6-Benzofuranyl psoralene-5-carboxylate(?).

6-Coumaranyl 2,3-dihydropsovalene-5-carboxylate(?) (0.5 g.) was refluxed in phenyl ether (10 ml.) with 10% palladium on charcoal (0.25 g.) for 5 hours. The hot solution was filtered to remove the catalyst, which was washed with a small amount of acetone. The acetone washings and phenyl ether were removed by steam distillation, and the dried, non-volatile residue was recrystallized from ethanol; yield 0.25 g. (49%), m.p. 228-230°.

Anal. Calcd. for  $C_{20}H_{10}O_6$ : C, 69.4; H, 2.89.  
Found: C, 69.1; H, 3.19.

6-Benzofuranyl 6-methylpsoralene-5-carboxylate(?).

6-Coumaranyl 2,3-dihydro-6-methylpsoralene-5-carboxylate(?) (0.65 g.) was refluxed in phenyl ether (12 ml.) with 10% palladium on charcoal (0.3 g.) for 5 hours. The hot solution was filtered to remove the catalyst. The catalyst was washed with a small amount of acetone

and the acetone was then removed from the filtrate by setting the beaker in front of a hot air fan. The residual phenyl ether solution was added to 300 ml. of petroleum ether (b.p. 60-71°). This mixture was kept at -10° for 24 hours and the precipitated product collected. The crude product was recrystallized from dilute ethanol; yield 0.26 g. (40%), m.p. 210-212°.

Anal. Calcd. for  $C_{21}H_{12}O_6$ : C, 70.1; H, 3.33.

Found: C, 70.1; H, 3.52.

7-(2-Oxoethoxy)-4-methylcoumarin. 7-Allyloxy-4-methylcoumarin (2 g.) was dissolved in 80 ml. of ethylene chloride. The solution was cooled to zero degrees in an ice bath and a stream of approximately 3% ozonized oxygen was passed through the solution at a rate of about 50 ml. per minute for 3 hours. The solution was then added to 100 ml. of 10% acetic acid containing zinc dust (0.8 g). The ethylene chloride was removed by evaporating the solution on a hot plate and the remaining hot aqueous solution filtered to remove the unused zinc. The product was collected from the thoroughly chilled filtrate; yield 1.4 g. This material contained approximately one mole of water. It was recrystallized, and at the same time dried by dissolving the hydrate in 50 ml. of xylene, followed by boiling the solution until it was concentrated

to two-thirds of its original volume. The product was improved by treatment with decolorizing charcoal; yield 0.9 g. (45%), m.p. 150-152°.

Anal. Calcd. for  $C_{12}H_{10}O_4 \cdot H_2O$ : C, 61.0; H, 5.08.  
Found: C, 61.8; H, 5.08.

Anal. Calcd. for  $C_{12}H_{10}O_4$ : C, 66.1; H, 4.58.  
Found: C, 66.1; H, 4.62.

The 2,4-dinitrophenylhydrazone melted at 229-231°.

Anal. Calcd. for  $C_{18}H_{14}O_7N_4$ : C, 54.3; H, 3.52;  
N, 14.1. Found: C, 54.6; H, 3.71; N, 14.3.

7-(2-Oxoethoxy)-coumarin. 7-Allyloxy coumarin (1 g.) was dissolved in 40 ml. of ethylene chloride. The solution was cooled to zero degrees with an ice bath and a stream of approximately 3% ozonized oxygen allowed to bubble through the solution at a rate of about 50 ml. per minute for 1.5 hours. The ethylene chloride solution was then added to 50 ml. of 10% acetic acid containing zinc dust (0.4 g.). The ethylene chloride was removed by evaporation on a hot place and the remaining hot aqueous solution filtered to remove the unused zinc. The product was collected from the thoroughly chilled filtrate; yield 0.65 g. This material contained approximately one mole of water. It was recrystallized, and at the same time dried by dissolving the hydrate in 30 ml. of xylene,

followed by boiling the solution until it was concentrated to two-thirds of its original volume. The product was improved by treatment with decolorizing charcoal; yield 0.37 g. (37%), m.p. 130-131°.

Anal. Calcd. for  $C_{11}H_8O_4 \cdot H_2O$ : C, 59.4; H, 4.51.  
Found: C, 60.2; H, 4.52.

Anal. Calcd. for  $C_{11}H_8O_4$ : C, 64.7; H, 3.93.  
Found: C, 64.8; H, 4.06.

7-(2-Bromoethoxy)-4-methylcoumarin. Absolute ethanol (150 ml.) containing sodium ethoxide prepared from 1.15 g. of sodium, was added to a 150 ml. anhydrous alcoholic solution in which were dissolved 4-methylumbelliferone (9.5 g.) and ethylene bromide (9.4 g.). This mixture was stirred and refluxed for 18 hours; the hot solution was then filtered and the filtrate added to twice its volume of water. The aqueous solution was then acidified with dilute hydrochloric acid to precipitate the product, which was then collected. The product was recrystallized from 40% ethanol; yield 2.5 g. (20%), m.p. 109-110°.

Anal. Calcd. for  $C_{12}H_{11}O_3Br$ : C, 50.7; H, 3.89.  
Found: C, 51.1; H, 3.99.

7-(2,3-Dihydroxypropoxy)-4-methylcoumarin.

7-Allyloxy-4-methylcoumarin (4.32 g.) was dissolved in 75 ml. acetone. To this acetone solution was added, with rapid stirring, over a 10-minute period, a chilled solution of potassium permanganate (2.1 g.) in water (400 ml.). An excess of ice was maintained in the reaction mixture during oxidation to assure a low reaction temperature. Upon completion of the permanganate addition, the stirring was continued for an additional 10 minutes. Sulfur dioxide was then bubbled into the brown mixture until all color had been discharged. Upon filtration of the mixture 2.2 g. of unchanged starting material was recovered. The filtrate was concentrated to a volume of 150 ml. and then extracted with three 60-ml. portions of ethyl acetate. The combined ethyl acetate fractions were evaporated to dryness and the residue recrystallized from water; yield 1.3 g. (26%), m.p. 108-110°.

Anal. Calcd. for  $C_{13}H_{14}O_5$ : C, 62.4; H, 5.61.  
Found: C, 62.6; H, 5.76.

7-(2-Oxoethoxy)-4-methylcoumarin. One gram of 7-(2,3-dihydroxypropoxy)-4-methylcoumarin was dissolved in 250 ml. of warm water. This solution was cooled to room temperature and a solution containing 0.92 g. of

periodic acid ( $\text{H}_5\text{IO}_6$ ) in 25 ml. of water was added. After stirring this mixture for 1.5 hours the white product which formed was removed by filtration and crystallized from dilute ethanol to yield 0.73 g. (77%) of the aldehyde. The product from this reaction, as judged by carbon and hydrogen analysis, appeared to be hydrated. It was dissolved in 30 ml. of xylene and the solution boiled on a hot plate until one-third of the xylene had evaporated. The hot xylene solution was then filtered. Analysis of the product crystallized from the chilled filtrate showed the compound to be anhydrous.

Anal. Calcd. for  $\text{C}_{12}\text{H}_{10}\text{O}_4$ : C, 66.1; H, 4.58.

Found: C, 66.2; H, 4.63.

Attempted cyclizations of 7-(2-oxoethoxy)-4-methylcoumarin.

1. 7-(2-Oxoethoxy)-4-methylcoumarin (1.09 g.) was added to 25 ml. absolute ethanol containing sodium ethoxide prepared from 0.115 g. of sodium. The mixture was warmed intermittently on a steam bath over a 30-minute period and the resultant dark solution was cooled and added to 50 ml. of water. After acidification with dilute hydrochloric acid the solution was concentrated to half its volume and cooled. The precipitated product was collected, decolorized with charcoal and

crystallized from water; yield 0.2 g., m.p. 183-184°. A mixed melting point with 4-methylumbelliferone showed no depression. The infrared spectrum was identical with that of an authentic sample of 4-methylumbelliferone.

Anal. Calcd. for  $C_{10}H_8O_3$ : C, 68.2; H, 4.54.  
Found: C, 68.2; H, 4.59.

2. 7-(2-Oxoethoxy)-4-methylcoumarin (0.5 g.) was added to 3 ml. of 48% hydrobromic acid, the mixture being refluxed, with stirring, for one hour. The mixture was cooled and water added to the dark solution. The insoluble reaction products consisted of a white material along with a dark, tarry residue. The aqueous phase containing the white suspended material was decanted from the tarry residue. The suspension was filtered and the precipitate twice recrystallized from water to yield 0.11 g. of compound melting at 183-184°. A mixed melting point with 4-methylumbelliferone gave no depression. Attempts to isolate a characterizable compound from the colored, tarry residue in the reaction flask failed.

Anal. Calcd. for  $C_{10}H_8O_3$ : C, 68.2; H, 4.54.  
Found: C, 68.2; H, 4.69.



7,8-Diallyloxy-4-methylcoumarin. 7,8-Dihydroxy-4-methylcoumarin (3.84 g.) was dissolved in acetone (80 ml.). Potassium carbonate (8.0 g.) and allyl bromide (5.32 g.) were added to the solution and the resulting mixture was stirred and refluxed for 18 hours. The acetone was removed by placing the open beaker containing the mixture in front of a hot air fan. The residue was dissolved in water and acidified with dilute hydrochloric acid. The solid which formed was removed from the aqueous phase by extraction with three portions of ethyl acetate. The ethyl acetate fractions were evaporated and the residue crystallized from ethyl alcohol. The chilled ( $-10^{\circ}$ ) alcohol solution yielded 4.2 g. of product, m.p.  $50-51^{\circ}$ .

Anal. Calcd. for  $C_{16}H_{16}O_4$ : C, 70.2; H, 5.88.  
Found: C, 70.6; H, 6.06.

7,8-Bis(2-oxoethoxy)-4-methylcoumarin. 7,8-Diallyloxy-4-methylcoumarin (1.5 g.) was dissolved in ethylene chloride (60 ml.) and the solution cooled to zero degrees with an ice bath. Approximately 3% ozonized oxygen was bubbled through the solution for 4 hours at the rate of about 50 ml. per minute. This solution was poured into 50 ml. 10% acetic acid containing 0.6 g. zinc dust and the ethylene chloride layer was removed by



evaporation on a hot plate. The remaining hot, aqueous solution was filtered and chilled. The product was collected and recrystallized from water; yield 0.82 g. (54%), m.p. 95-97°.

Anal. Calcd. for  $C_{14}H_{12}O_6$ : C, 60.8; H, 4.35.  
Found: C, 61.2; H, 4.51.

Attempted cyclizations of 7-(2-bromoethoxy)-4-methylcoumarin.

1. An intimate mixture of 7-(2-bromoethoxy)-4-methylcoumarin (0.5 g.) and anhydrous zinc chloride (0.5 g.) were heated at 220° for 15 minutes. After cooling, the fused mass was partitioned between water and ethyl acetate. The ethyl acetate fraction was evaporated to dryness and the residue was crystallized from dilute ethanol; yield 0.25 g., m.p. 183-185°. A mixed melting point with 4-methylumbelliferone gave no depression.

Anal. Calcd. for  $C_{10}H_8O_3$ : C, 68.2; H, 4.54.  
Found: C, 67.9; H, 4.69.

2. 7-(2-Bromoethoxy)-4-methylcoumarin (0.5 g.) and aluminum chloride (1 g.) were added to 40 ml. of anhydrous methylene chloride. This mixture was refluxed, under anhydrous conditions, for 6 hours and then allowed to stand at room temperature for an additional 2 hours.

Then 40 ml. of 20% hydrochloric acid was added to this mixture and the methylene chloride layer was removed by evaporation on a steam bath. The remaining water solution was concentrated, chilled and the precipitated product collected. Decolorization and recrystallization from dilute ethanol yielded 0.1 g., m.p. 184-185°. A mixed melting point with 4-methylumbelliferone gave no depression.

Anal. Calcd. for  $C_{10}H_8O_3$ : C, 68.2; H, 4.54.

Found: C, 67.9; H, 4.69.

Diacetyl acylal 7-(2-oxoethoxy)-4-methylcoumarin.

A solution containing 7-(2-oxoethoxy)-4-methylcoumarin (0.5 g.), acetic anhydride (5 ml.) and 48% hydrobromic acid (0.5 ml.) was refluxed for 3.5 hours. The mixture was then added to 20 ml. of water, brought to a boil, decolorized with charcoal, filtered and cooled. The rapidly formed crystals were collected and recrystallized from ethanol; yield 0.4 g. (55%), m.p. 129-130°.

Anal. Calcd. for  $C_{16}H_{16}O_7$ : C, 60.0; H, 5.00.

Found: C, 60.2; H, 5.15.

2,5-Bis-[(7-methyleneoxy)-4-methylcoumarin]-p-dioxane(?). A solution containing sodium ethoxide was prepared by reacting sodium (1.15 g.) with 250 ml. of

absolute ethanol. 4-Methylumbelliferone (8.8 g.) and epichlorohydrin (4.63 g.) were added to this alcoholic solution and the mixture then refluxed, with stirring, for 3 hours. The hot mixture was then filtered and the ethanolic filtrate cooled overnight in a refrigerator. The product was collected and recrystallized from ethanol; yield 3.1 g. (27%), m.p. 187-189°.

Anal. Calcd. for  $C_{26}H_{24}O_8$ : C, 67.2; H, 5.17.

Found: C, 66.8; H, 5.17.

## SUMMARY

A brief discussion of the history, occurrence, synthesis, and pharmacological properties of xanthotoxin has been given.

A discussion of present synthetic routes to the psoralenes has been presented.

The synthesis of a number of 5- and 5,6-disubstituted 2,3-dihydropsoalenes and the corresponding dehydrogenated products (in most cases) has been reported along with a new synthesis of psoralene.

An attempt to synthesize psoralenes beginning with the umbelliferone moiety of the molecule has resulted in the successful preparation of the desired intermediates. Every attempt to cyclize these intermediates to psoralenes has been unsuccessful.

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