authentic sample of 2-(β-naphthyl)-benzo[h]quinoline-4-carboxylic acid was prepared by the condensation of α-naphthisatin with 2-acetonaphthone[4] and purified by the aforementioned method[5]; m.p. 248–250°; mixed m.p. of the authentic sample with compound VI 248–250°.

Fraction II: *racemic 1-(β-naphthyl)ethylurea.* Fraction II was thrice recrystallized from 3-pentanone, m.p. 198–200°; mixed m.p. with an authentic sample of racemic 1-(β-naphthyl)ethylurea, 198–200° (lit.,[6] m.p. 196–198°).

Infrared spectrum of II (potassium bromide): 3435(S), 3350(S), 3230(M), 3070(W), 2990(W), 2930(W), 1681(W), 1648(S), 1618(W), 1460(W), 1384(M), 1341(W), 1330(W), 1301(W), 1276(W), 1252(W), 1182(M), 1145(M), 1128(M), 1055(W), 1019(W), 968(W), 954(W), 909(W), 896(W), 878(W), 860(W), 825(S), 775(W), 750(S), 662(M).

The infrared spectrum of authentic 1-(β-naphthyl)ethylurea was identical with that of compound II.

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.86; H, 6.59; N, 13.08; O, 7.47. Found: C, 72.56; H, 6.62; N, 13.12; O, 7.81.

Fraction III: *3-methylbenzo[f]phthalimidine.* Fraction III was recrystallized from benzene-ethanol and from chloroform; m.p. 236–240°.

Anal. Calcd. for $C_{13}H_{11}NO$: C, 78.80; H, 5.65; N, 7.10. Found: C, 78.90; H, 6.23; N, 6.97.

Infrared spectrum of III(potassium bromide): 3310(W), 3050(W), 3005(W), 2960(W), 2905(W), 1708(M), 1690(S), 1598(W), 1550(W), 1535(W), 1505(W), 1455(W), 1378(W), 1345(W), 1273(W), 1216(S), 1127(W), 1016(W), 950(W), 887(W), 855(W), 817(M), 752(S), 663(W).

Fraction IV: *sym-di-1-(β-naphthyl)ethylurea.* Fraction IV was recrystallized from ethanol; m.p. 226–230°. Further purification by chromatography on alumina using benzene–ethyl acetate (1:1) as developer gave a pure compound, m.p. 229–231°.

Anal. Calcd. for $C_{25}H_{24}N_2O$: C, 81.51; H, 6.57; N, 7.61; mol. wt., 368. Found: C, 81.61; H, 6.89; N, 7.52; mol. wt. (Rast) 394.

Infrared spectrum of IV (potassium bromide); 3300(S), 3035(W), 2955(M), 1625(S), 1596(sh), 1578(sh), 1562(S), 1504(W), 1450(W), 1373(S), 1325(M), 1291(W), 1272(W), 1236(S).

VANCOUVER 8, CANADA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Psoralenes. III. Cyclization Studies of Certain Substituted Coumarins and Coumarans[1]

ROBERT C. ESSE AND BERT E. CHRISTENSEN

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The synthesis of a series of new 5,6-dialkyl-2,3-dihydropsoralenes is described along with the dehydrogenation of these derivatives to the corresponding psoralenes. A compound which may be the 6-coumaranyl ester of 2,3-dihydro-5-carboxypsoralene was prepared. This compound was dehydrogenated and also converted to the free acid. The free acid was also synthesized directly by a Pechmann type reaction. This acid was simultaneously decarboxylated and dehydrogenated to psoralene. An isomer of xanthotoxin, 5-methoxypsoralene, was prepared from the corresponding 2,3-dihydro derivative. 5-Acetoxypsoralene was prepared; this compound was stable toward dehydrogenation in contrast to 5-hydroxypsoralene which has been reported to decompose under dehydrogenation operations. The synthesis of a number of coumarin derivatives which might serve as intermediates for the preparation of psoralenes was accomplished. Extensive attempts to cyclize two of these intermediates, 7-(2-oxoethoxy)-4-methylcoumarin and 7-(2-bromoethoxy)-4-methylcoumarin, were unsuccessful. In several of the cyclization experiments where a pure product was isolated it was found that ether cleavage to 4-methylumbelliferone rather than ring closure had taken place.

In recent years the furocoumarin xanthotoxin has received considerable attention, both in the scientific literature[2] and the popular press. As xanthotoxin (9-methoxypsoralene) is obtained from natural sources and the number of known psoralenes are limited, it was worthwhile to investigate the procedures for the synthesis of these potential drugs as well as to prepare a number of new psoralenes for research purposes.

The starting material for the synthesis of psoralene compounds is resorcinol or its 2- or 5-substituted derivative. Two routes are available either (1) *via* conversion to 6-hydroxycoumaran, I (2,3-dihydro-6-hydroxybenzofuran) or (2) by way of 7-hydroxycoumarin, II (umbelliferone) (see Fig. 1).

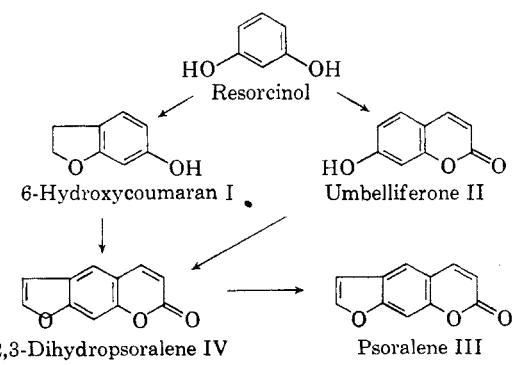

Fig. 1. Synthesis of psoralene from resorcinol

(1) This work was supported in part by grants from the Division of Research Grants and Fellowships, National Institutes of Health, Public Health Service. Published with the approval of the Monographs Publications Committee, Oregon State College as Research Paper No. 381, School of Science, Department of Chemistry.

(2) M. B. Salzberger and B. Lerner, *J. Am. Med. Assn.*, **167**, 2077 (1958). A. B. Lerner, J. Invest. Dermatol., **25**, 1 (1955). T. B. Fitzpatrick, *et al.*, J. Invest. Dermatol. **25**, 187 (1955). T. B. Fitzpatrick, J. D. Imbrie, and D. Labby, *J. Am. Med. Assn.*, **167**, 1586 (1958).

The earliest work was that of Späth,[3] who in a one step operation condensed malic acid with 6-hydroxycoumaran in a sulfuric acid medium to yield 2,3-dihydropsoralene IV from which psoralene III was obtained by dehydrogenation (see Fig. 2). Later Horning and Reisner[4] made this approach more attractive by devising an improved synthesis of the key intermediate 6-hydroxycoumaran. Furthermore, these workers found that 6-acetoxycoumaran (an intermediate for the preparation of 6-hydroxycoumaran) could be used directly for the synthesis of the 5-substituted 2,3-dihydropsoralenes and by condensing it with a variety of β-ketoesters, they obtained a series of 5-substituted 2,3-dihydropsoralenes.

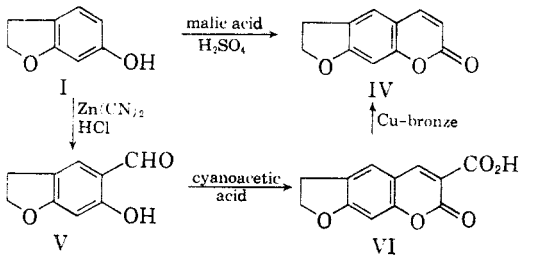

Fig. 2. Synthesis of psoralene from 6-hydroxycoumaran

Robinson, *et al.*[5] also using 6-hydroxycoumaran as the key intermediate devised an alternate route for the synthesis of psoralene. This group formylated I in the 5-position and then condensed the product V with cyanoacetic acid to yield a psoralene compound (see Fig. 2). The resulting 6-carboxy-2,3-dihydropsoralene VI was then decarboxylated and dehydrogenated to yield psoralene itself.

Ray, *et al.*[6] have approached the problem of furocoumarin synthesis from the coumarin moiety of the psoralene molecule and report the synthesis of 3-methylpsoralene. In this procedure 7-acetonyloxycoumarin, VIII, was prepared by treating umbelliferone with chloroacetone. Cyclization of this intermediate to IX 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 (see Fig. 3).

An alternate route employing a coumarin intermediate was devised by Rodighiero and Antonello[7] for the synthesis of xanthotoxin, IX. These workers converted 7-hydroxy-8-methoxycoumarin to the 6-formyl derivative which in turn was cyclized to the psoralene using ethyl bromoacetate to effect ring closure. The four synthetic routes to the psoralenes of which two are based on the use of umbelliferone and two on the use of 6-hydroxycoumaran are illustrated in Figs. 2 and 3.

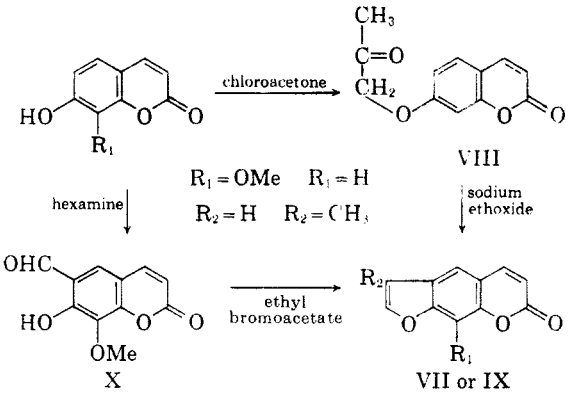

Fig. 3. Synthesis of psoralene from umbelliferone

Three of the routes (see Figs. 2 and 3 — the two employing formylation procedures and the third, the β-ketoester condensation) are long and involved. On the other hand the fourth procedure, as reported by Ray,[6] requires only three steps from resorcinol to a 3-substituted psoralene (see Fig. 3). This method is also attractive in that an umbelliferone is an intermediate rather than 6-hydroxycoumaran. Umbelliferones can be synthesized both easily and in some variety.[8]

The second step of Ray's procedure simply involves the coupling of an α-haloketone and an umbelliferone (see Fig. 3) to form an ether *via* the Williamson procedure. The formation of the keto derivative proceeds smoothly; the ring closure, however, in our hands was not satisfactory giving at best only 4% yield (Ray did not report yield data for this step).

Even if ring closure were to proceed in good yield, Ray's method is restrictive in that it yields 3-methylpsoralene (see VII, Fig. 3). To prepare the unsubstituted psoralene by the Ray procedure it would be necessary to start with 7-(2-oxoethoxy)-coumarin.

Although monochloroacetone reacted with umbelliferone *via* a Williamson synthesis to yield the desired intermediate, chloroacetaldehyde would not react under similar conditions with 4-methylumbelliferone. For this reason the 7-(2-oxoethoxy)-4-methylcoumarin was prepared by oxidative procedures from both 7-(allyloxy)- and 7-(2,3-dihydroxypropoxy)-4-methylcoumarin.

Cyclization experiments using 7-(2-oxoethoxy)-4-methylcoumarin were undertaken using both acid and basic catalyst, all of which led to either (1) recovery of starting material, (2) an uncharacterizable tar, or (3) ether cleavage with the recovery of 4-methylumbelliferone. One experiment

(3) E. Späth and M. Pailer. *Ber.*, **67**, 1212 (1934).

(4) E. C. Horning and D. B. Reisner, *J. Am. Chem. Soc.*, **70**, 3619 (1948).

(5) R. T. Foster, A. Robinson, and (in part) A. Bushra, *J. Chem. Soc.*, 2254 (1948).

(6) N. Ray, S. S. Silooja, and V. R. Vaid, *J. Chem. Soc.*, 812 (1935).

(7) G. Rodighiero and C. Antonello, *Annali di Chimica (Rome)* **46**, 960 (1956) [abstracted in *Chem. Abstr.*, **51**, 6616 (1957)].

(8) S. Sethna and R. Phadke, *Org. Reactions*, **7**, 1 (1953).

using acetic anhydride with 48% hydrobromic acid yielded the acylal derivative of 7-(2-oxoethoxy)-4-methylcoumarin. In connection with these ring closure studies both 7-bromoethoxy-4-methylcoumarin and 7,8-di(2-oxoethoxy)-4-methylcoumarin were synthesized and their preparations are included herewith for purposes of documentation.

For this reason a new series of experiments were undertaken using 6-acetoxycoumaran as the intermediate and based on the procedures described by Horning and Reisner.[4] A series of 6-alkyl-2,3-dihydro-5-methylpsoralenes were prepared by condensing the appropriate α-alkyl-β-ketoesters with 6-acetoxycoumaran. 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

In an attempt to prepare 5-carboxy-2,3-dihydropsoralene, XI, the sodium salt of diethyl oxalacetate was treated 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 resulted, from which no pure component could be isolated. However, as the authors became more experienced with the reaction, conditions were discovered 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 of the 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 carboxylic acid 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. Furthermore, when $C_{20}H_{14}O_6$ was subjected to the aforementioned treatment in 75% sulfuric acid medium, the *desired compound*, 5-carboxy-2,3-dihydropsoralene, was isolated from the reaction mixture. Speculations based on this data indicated that the sequence of reactions responsible for these changes may be that shown in Fig. 4. However, experiments designed to confirm the hypothesis that $C_{20}H_{14}O_6$ was the ester 6-coumaranyl

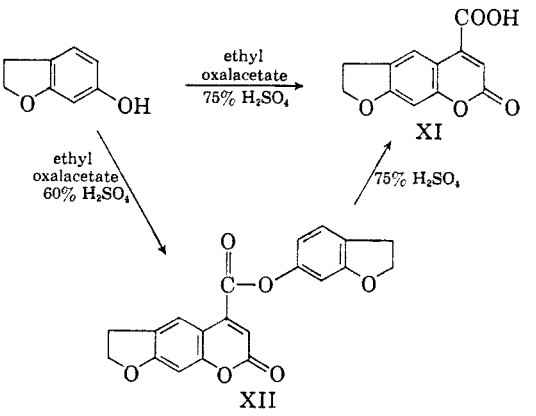

Fig. 4. 5-Carboxy-2,3-dihydropsoralene *via* the $C_{20}H_{14}O_6$, XII, compound

2,3-dihydropsoralene-5-carboxylate, XII, were inconclusive. Repeated attempts to saponify the compound under various conditions of basic hydrolysis were unsuccessful thus leaving the question of structure unsettled.

Horning and Reisner[9] have obtained psoralene by the simultaneous decarboxylation and dehydrogenation of 6-carboxy-2,3-dihydropsoralene. Similar treatment of the 5-carboxy-2,3-dihydropsoralene prepared in this laboratory yielded the expected, unsubstituted psoralene.

5-Hydroxypsoralene was one of the psoralenes desired for research purposes by this laboratory. Horning and Reisner[9] had succeeded in preparing the 2,3-dihydro-5-hydroxypsoralene from a phloroglucinol intermediate (in place of resorcinol—see Fig. 1) but were unable to dehydrogenate the compound. In this laboratory the 2,3-dihydro-5-hydroxypsoralene was converted to both the 5-acetoxy- and 5-methoxy- derivatives and each subjected to dehydrogenation operations. The 5-acetoxy derivative was stable under the conditions of dehydrogenation, but the 5-methoxy derivative responded readily to yield one of the desired isomers of xanthotoxin.

EXPERIMENTAL

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-min. 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 min. 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°.

(9) E. C. Horning and D. B. Reisner, *J. Am. Chem. Soc.*, **72**, 1514 (1950).

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.4; H, 5.65. Found: C, 62.6; H, 5.76.

7-(2-Oxoethoxy)-4-methylcoumarin. A. 7-Allyloxy-4-methylcoumarin (2 g.) was dissolved in 80 ml. of ethylene chloride. The solution was cooled to 0° 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 min. for 3 hr. 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 1 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, 5.13. Found: C, 61.8; H, 5.08.

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.1; H, 4.62. 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, 3.54; N, 14.1. Found: C, 54.6; H, 3.71; N, 14.3.

B. 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 in 25 ml. of water was added. After stirring this mixture for 1.5 hr. 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 $C_{12}H_{10}O_4$: C, 66.1; H, 4.62. Found: C, 66.2; H, 4.63.

7-(2-Oxoethoxy)coumarin. 7-Allyloxycoumarin (1 g.) was dissolved in 40 ml. of ethylene chloride. The solution was cooled to 0° 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 min. for 1.5 hr. 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 plate 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 1 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, 4.04. Found: C, 60.2; H, 4.52.

Anal. Calcd. for $C_{11}H_8O_4$: C, 64.7; H, 3.95. Found: C, 64.8; H, 4.06.

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 hr. 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°) alcohol solution yielded 4.2 g. of product, m.p. 50–51°.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.6; H, 5.93. Found: C, 70.6; H, 6.06.

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 hr.; 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, 50.9; H, 3.92. Found: C, 51.1; H, 3.99.

7,8-Di(2-oxoethoxy)-4-methylcoumarin. 7,8-Diallyloxy-4-methylcoumarin (1.5 g.) was dissolved in ethylene chloride (60 ml.) and the solution cooled to 0° with an ice bath. Approximately 3% ozonized oxygen was bubbled through the solution for 4 hr. at the rate of about 50 ml. per min. This solution was poured into 50 ml. of 10% acetic acid containing 0.6 g. of 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, 4.38. Found: C, 61.2; H, 4.51.

7-(2,2-Diacetoxyethoxy)-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 hr. 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, 5.04. Found: C, 60.2; H, 5.15.

2,3-Dihydro-5,6-dimethylpsoralene. A mixture containing 6-acetoxycoumaran (1.78 g.) and ethyl α-methylacetoacetate (1.42 g.) was placed on a steam bath; 10 ml. of 75% sulfuric acid was added with stirring over a 10-min. 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, 5.60. Found: C, 72.2; H, 5.60.

2,3-Dihydro-6-ethyl-5-methylpsoralene. 6-Acetoxycoumaran (1.78 g.) and ethyl α-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, 6.13. Found: C, 72.5; H, 6.12.

2,3-Dihydro-6-isopropyl-5-methylpsoralene. 6-Acetoxycoumaran (1.76 g.) and ethyl α-isopropylacetoacetate (1.72 g.) were treated in the same manner as 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, 6.61. Found: C, 73.6; H, 6.84.

2,3-Dihydro-5-methyl-6-myristylpsoralene. Eight milliliters of 75% sulfuric acid was added dropwise to a stirred mixture of 6-acetoxycoumaran (0.89 g.) and ethyl α-myristylacetoacetate (1.63 g.). The reaction was started at room temperature and gradually brought to 65°. After 2 hr. the mixture was cooled and poured onto ice. The precipitate was

TABLE I

5,6-Dialkylpsoralenes

Psoralenes	Yield, %	M.P.	Formula	Carbon, %		Hydrogen, %	
				Calcd.	Found	Calcd.	Found
5,6-Dimethyl-	45	235–236°	$C_{13}H_{10}O_3$	72.9	72.9	4.71	4.61
6-Ethyl-5-methyl-	55	179–180°	$C_{14}H_{12}O_3$	73.7	73.4	5.30	5.40
6-Isopropyl-5-methyl-	44	145–147°	$C_{15}H_{14}O_3$	74.3	74.0	5.83	5.89

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, 9.62. Found: C, 77.9; H, 9.54.

Dehydrogenation of the 5,6-dialkyl-2,3-dihydropsoralenes. 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 hr. 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 nonvolatile residue was collected, decolorized with charcoal, and crystallized from ethanol. See Table I.

Reaction product of 6-acetoxycoumaran and diethyl sodiooxalacetate (6-coumaranyl 2,3-dihydropsoralene-5-carboxylate, XII). 6-Acetoxycoumaran (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-min. period. Stirring was continued for another 30 min. and the mixture then replaced on a steam bath for an additional 15 min. 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, 4.03. Found: C, 68.4; H, 4.23.

Dehydrogenation product (6-benzofuranyl psoralene-5-carboxylate). The condensation product $C_{20}H_{14}O_6$ (0.5 g.) was refluxed in phenyl ether (10 ml.) with 10% palladium on charcoal (0.25 g.) for 5 hr. 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, nonvolatile 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, 2.91. Found: C, 69.1; H, 3.19.

2,3-Dihydropsoralene-5-carboxylic acid, XI. A. 6-Acetoxycoumaran (3.56 g.) was melted and stirred into a paste with the sodium salt of diethyl oxalacetate (4.60 g.). Twenty milliliters of 75% sulfuric acid was added over a 30-min. period. The temperature was then raised to 80° and the stirred mixture maintained at this temperature for an additional 30 min.; 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, 3.48. Found: C, 62.2; H, 3.73.

B. The compound $C_{20}H_{14}O_6$, XII (0.5 g.), was added to 75% sulfuric acid (3 ml.) and the mixture was stirred for 25 min. at room temperature. The temperature was then raised to 80° and maintained at this temperature while stirring was continued an additional 25 min. 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, 3.48. Found: C, 62.5; H, 3.69.

Psoralene. 2,3-Dihydropsoralene-5-carboxylic acid, XI (0.5 g.), and 0.25 g. of 10% palladium on charcoal were refluxed in 10 ml. of phenyl ether for 5 hr. 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°, 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, 3.25. Found: C, 70.6; H, 3.42.

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

Ethyl α-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 2-hr. 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, 11.75. Found: C, 73.5; H, 11.41.

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 hr., 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, 4.10. Found: C, 63.4; H, 4.27.

2,3-Dihydro-5-methoxypsoralene. One and a half grams of 2,3-dihydro-5-hydroxypsoralene[8] in 50 ml. of acetone was refluxed with potassium carbonate (3.75 g.) and dimethyl sulfate (1.5 ml.) for 18 hr. 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, 4.62. Found: C, 66.0; H, 4.78.

5-Methoxypsoralene. 2,3-Dihydro-5-methoxypsoralene (0.63 g.) was dehydrogenated by the general procedure as 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, 3.73. Found: C, 66.5; H, 3.91.

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