piperidinomethyl-4-keto-1,3,3a,7-tetrazaindene (V), and bis(6-methyl-4-oxo-1,3,3a,7-tetrazainden-7-yl)-methane (VI). The reaction was not investigated further.

EXPERIMENTAL

Method A. A mixture of 1 equivalent of 4-chloro-6-methyl-1,3,3a,7-tetrazaindene[1b] (I), 3 equivalents of the amine, and ten parts by volume of ethanol was refluxed for 2 hr., and then cooled. The solid was either collected or the reaction mixture evaporated to dryness, depending on the solubility of the product in ethanol.

Method B. It was carried out in the same manner as Method A except that the reactants were allowed to stand at room temperature for 2 hr., rather than being refluxed.

Method C. A mixture of 1 equivalent of I, 1 equivalent of the amine, and 1.5 equivalents of triethylamine in ten parts by volume of ethanol was refluxed 2 hr. and then evaporated to dryness.

Method D. Acetonitrile was employed in place of ethanol in Method A.

Method E. Equivalent amounts of I, amine, and sodium bicarbonate in seven parts by volume of nitrobenzene were refluxed 2 hr. and the solid was collected and washed with water and ether.

6-Methyl-7-piperidinomethyl-4-keto-1,3,3a,7-tetrazaindene. Piperidine (2.8 g.) was dissolved in 2.5 ml. of 40% formalin. After the exothermic reaction had subsided, 4.5 g. of 6-methyl-4-oxo-1,3,3a,7-tetrazaindene (IV) was added, followed by the addition of 25 ml. of ethanol. After a 1-min. reflux, solution was complete; in 10 min., a white precipitate settled out. Reflux was continued for 30 min. more. After cooling, the product was collected and then crystallized from alcohol to give 4 g. of V, m.p. 230°.

Anal. Calcd. for $C_{12}H_{17}ON_5$: C, 58.2; H, 6.9. Found: C, 58.7; H, 6.9.

In one run, an insufficient quantity of piperidine was used and a product which had an analysis corresponding to bis(6-methyl-4-oxo-1,3,3a,7-tetrazainden-7-yl)methane (VI), m.p. 310°, was obtained.

Anal. Calcd. for $C_{13}H_{12}O_2N_8$: C, 50.0; H, 3.9; N, 35.9. Found: C, 50.5; H, 4.0; N, 35.7.

ROCHESTER 4, N. Y.

[CONTRIBUTION FROM THE DYSON-PERRINS LABORATORY]

Synthetic Furocoumarins. I. A New Synthesis of Methyl-substituted Psoralenes and Isopsoralenes

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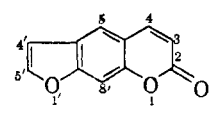
Received May 13, 1960

Three methyl-substituted psoralenes and two methyl-substituted isopsoralenes have been synthesized by a new method from *o*-allyl-7-hydroxycoumarins by acetylation, bromination, and cyclization in a basic medium. 7-Allyloxycoumarins undergo Claisen rearrangement to 8-allyl-7-hydroxycoumarins, which lead to methylated isopsoralenes. 7-Allyloxy-8-methylcoumarins rearrange to 6-allyl-7-hydroxy-8-methylcoumarins, which produce methylated psoralenes. 3-Allyloxyphenyl acetate gives a mixture of 2-allylresorcinol and 4-allylresorcinol on Claisen rearrangement followed by hydrolysis. The latter compound was converted to a dimethylpsoralene.

Naturally occurring furocoumarins have recently attracted attention because several of them alter the response of human skin to ultraviolet radiation.[3] In particular, xanthotoxin (8-methoxypsoralene) has been used clinically to prevent sun burning, to encourage sun tanning, and in the treatment of vitiligo.[3] Its effect on ultraviolet carcinogenesis has also been studied.[3,4] The erythema inducing activity of several synthetic furocoumarins has been studied in an effort to understand their biological mechanism of action.[5] The photosensitization of bacteria by a variety of furocoumarins (including some synthetic compounds) has also been reported.[6]

Several furocoumarin nomenclatures are currently in use and this has occasionally led to confusion.[7] Throughout this and later papers, structure I shall be designated psoralene and shall be numbered as shown, which is in accordance with the recommendation of the Food and Drug Administration.[7] Structure II shall be designated isopsoralene with a similar numbering system.[8]



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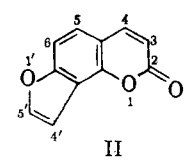

II

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(2) This investigation was made possible by the interest and advice of Sir Robert Robinson and by the support provided by a Fulbright Grant administered by the United States Educational Commission in the United Kingdom.

(3) Psoralenes and radiant energy, proceedings of a symposium. *J. Invest. Dermatol.*, **32**, 131–391 (1959).

(4) M. A. O'Neal and A. C. Griffin, *Cancer Research*, **17**, 911 (1957).

(5) (a) M. A. Pathak and T. B. Fitzpatrick, *J. Invest. Dermatol.*, **32**, 255 and 509 (1959); M. A. Pathak, J. B. Fellman, and K. D. Kaufman, *ibid.*, **35**, 165 (1960); (b) L. Musajo, *Farmaco (Pavia) Ed. sci.*, **10**, 3 (1955); L. Musajo, G. Rodighiero, G. Caporale, and C. Antonello, *Farmaco (Pavia) Ed. sci.*, **13**, 355 (1958).

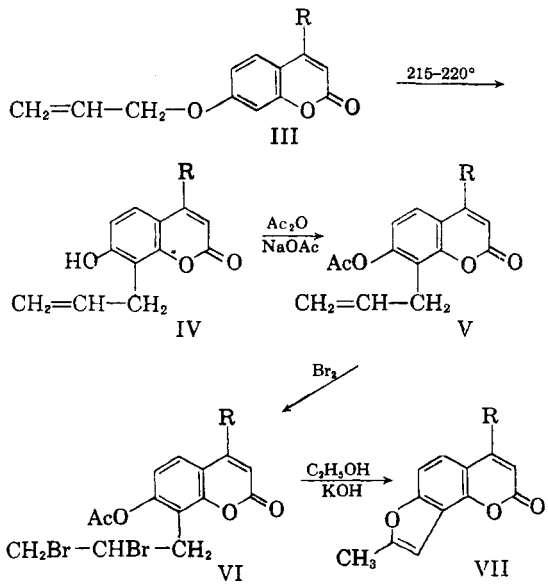
(6) W. L. Fowlks, D. G. Griffith, and E. L. Oginsky, *Nature*, **181**, 571 (1958).

(7) A. C. Curtis, *J. Invest. Dermatol.*, **32**, 133 (1959).

(8) *Chemical Abstracts* prefers δ-lactone of 6-hydroxy-5-benzofuranacrylic acid for I and δ-lactone of 4-hydroxy-5-benzofuranacrylic acid for II, but these names are not in common usage.

With a few exceptions, reported syntheses of furocoumarins have followed two general patterns. Most isopsoralenes and some psoralenes have been prepared from *o*-formyl- or *o*-acyl-7-hydroxycoumarins in three or four steps.[9] Although the latter steps usually run smoothly and give high yields, the *o*-formyl-7-hydroxycoumarins cannot be prepared in good yield and the *o*-acyl-7-hydroxycoumarins are produced by Fries rearrangements, which frequently give mixtures of isomeric products. The other general method is that of Spath,[10a] which has been modified for the synthesis of several psoralenes.[10b] It involves the preparation of dihydropsoralenes from 6-hydroxycoumarans, followed by dehydrogenation. An important disadvantage of this method is the final dehydrogenation step, which frequently gives poor yields.

This paper describes a new synthesis, involving *o*-allyl-7-hydroxycoumarins as intermediates, which has produced methyl-substituted psoralenes and isopsoralenes in quantities sufficient for biological evaluation[5a,6] and even clinical testing. The method is based on the known[11] conversion of *o*-(β,γ-dibromopropyl)phenyl acetate to 2-methylbenzofuran. Its application to the synthesis of isopsoralenes is illustrated by structures III through VII.



Two compounds, 5′-methylisopsoralene (VII, R = H) and 4,5′-dimethylisopsoralene (VII, R = CH_3), were prepared in this way. The 8-allyl-7-hydroxycoumarins (IV, R = H or CH_3) were obtained by heating 7-allyloxycoumarins (III, R = H or CH_3) at 215° to cause the Claisen rearrangement, as described by earlier workers.[12]

In each case, the 7-hydroxy group of IV was acetylated to minimize the possibility of ring bromination during the addition of one equivalent of bromine to the allyl double bond. Finally, the dibromo intermediates (VI, R = H or CH_3) were refluxed for two hours with alcoholic potassium hydroxide to give yields of methylated isopsoralenes (VII, R = H or CH_3) in excess of 50%. Although extensive studies were not carried out, the two-hour reflux period is optimal in the sense that one-hour and three-hour reflux periods resulted in reduced yields.

This method was applied to the synthesis of psoralenes by the use of 7-allyloxycoumarins with a methyl group blocking the reactive 8- position. Rangaswami and Seshadri[13] have already shown that 7-allyloxy-4,8-dimethylcoumarin (X, R = CH_3) rearranges to give 6-allyl-4,8-dimethyl-7-hydroxycoumarin (XI, R = CH_3) in good yield. It was found that 7-allyloxy-8-methylcoumarin (X, R = H) also rearranges smoothly to a 6-allyl derivative (XI, R = H). Both 6-allyl compounds were acetylated, brominated, and cyclized (as in the preparation of isopsoralenes) to give 4,5′,8-trimethylpsoralene (XII, R = CH_3) and 5′,8-dimethylpsoralene (XII, R = H). In the trimethylpsoralene case, the final cyclization step was conducted with sodium ethoxide instead of potassium hydroxide in ethyl alcohol. That modification gave a product which did not require decolorization with charcoal. The reflux time was reduced to one and three quarter hours, with fifteen minutes allowed for cooling, prior to the work-up.

One of the starting materials, 7-hydroxy-8-methylcoumarin (IX, R = H),[14] was prepared by an improved method, which involved condensation of malonic acid with 4-formyl-2-methylresorcinol (VIII)[15] under the conditions described by Vorsatz.[16] The resultant 7-hydroxy-8-methylcoumarin-3-carboxylic acid (IX, R = COOH) lost carbon dioxide to give an over-all 70% yield of 7-hydroxy-8-methylcoumarin, which had m.p. 258–259° instead of the reported[14] 231–232°. As in the preparation of the other 7-allyloxycoumarins,

(9) E. Spath and M. Pailer, *Ber.*, **68B**, 940 (1935); D. B. Limaye and D. D. Gangal, *Rasayanam*, **1**, 15 (1936) and D. B. Limaye, *Rasayanam*, **1**, 187 (1939); D. N. Shah and N. M. Shah, *J. Org. Chem.*, **19**, 1938 (1954); G. Rodighiero and C. Antonello, *Ann. chim.* (*Rome*), **46**, 960 (1956); C. Antonello, *Gazz. chim. ital.*, **88**, 415–433 (1958).

(10) (a) E. Spath, B. L. Manjunath, M. Pailer, and H. S. Jois, *Ber.*, **69B**, 1087 (1936). (b) E. C. Horning and D. B. Reisner, *J. Am. Chem. Soc.*, **70**, 3619 (1948) and **72**, 1514 (1950); C. Lagercrantz, *Acta Chem. Scand.*, **10**, 647 (1956); G. Caporale, *Farmaco* (*Pavia*) *Ed. sci.*, **13**, 784 (1958).

(11) L. Claisen, *Ann.*, **418**, 69 (1919) and *Ber.*, **53**, 322 (1920).

(12) (a) W. Baker and O. M. Lothian, *J. Chem. Soc.*, 628 (1935). (b) B. Krishnaswamy and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **13A**, 43–8 (1941).

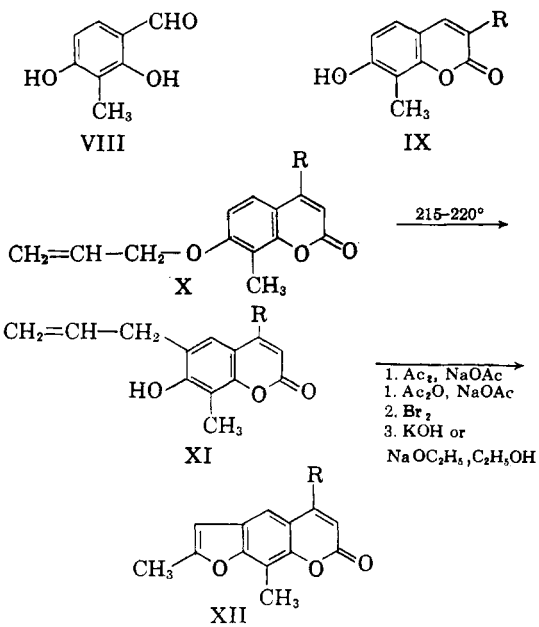
(13) S. Rangaswami and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **7A**, 8–12 (1938).

(14) T. R. Seshadri and V. Venkateswarlu, *Proc. Indian Acad. Sci.*, **14A**, 297 (1941).

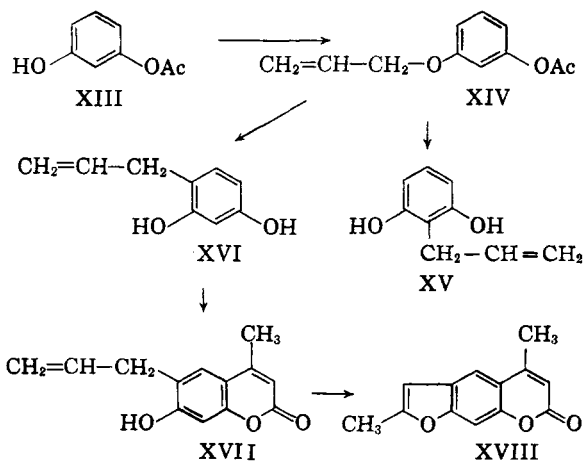
(15) W. Baker, H. F. Bondy, J. F. W. McOmie, and H. R. Tunnicliff, *J. Chem. Soc.*, 2835 (1949).

(16) F. Vorsatz, *J. prakt. Chem.*, **145**, 265 (1936).

which were already known, 7-hydroxy-8-methylcoumarin was treated with allyl bromide and potassium carbonate in acetone to give the unknown compound 7-allyloxy-8-methylcoumarin (X, R = H).



An important disadvantage of the new method, as applied to the synthesis of linear furocoumarins (psoralenes), is the necessity of having 7-allyloxycoumarins with a blocking group to prevent migration of the allyl group to the 8 position during Claisen rearrangement. With partial success, this difficulty has been eliminated by effecting the Claisen rearrangement before forming the coumarin ring system. Resorcinyl monoacetate (XIII) was converted to 3-allyloxyphenyl acetate (XIV) which underwent Claisen rearrangement on refluxing in diethylaniline[17] and, after alkaline hydrolysis, gave an oil, expected to be 4-allylresorcinol (XVI).[18] The oil reacted with ethyl acetoacetate in a Pechmann type condensation to give a mixture of the known[12a] 8-allyl-7-hydroxy-4-methylcoumarin (IV, R = CH_3) and its isomer, which must be 6-allyl-7-hydroxy-4-methylcoumarin (XVII). The two isomers were separated, with difficulty, by chromatography on an acid-washed alumina column. It is obvious that the oil is actually a mixture of 2-allylresorcinol (XV) and 4-allylresorcinol (XVI). Further study on the preparation of pure 4-allylresorcinol is in progress. The small quantity of 6-allyl-7-hydroxy-4-methylcoumarin (XVII) actually isolated, was enough to convert to 4,5′-dimethylpsoralene (XVIII) by the method already described.



While the present work was in progress, there was reported[19] the synthesis of a small quantity of isopsoralene by a method involving ozonolysis of 8-allyl-7-hydroxycoumarin (IV, R = H) which further emphasizes the value of *o*-allyhydroxycoumarins as intermediates in the synthesis of furocoumarins.

EXPERIMENTAL

Full details of the four step process of converting a 7-allyloxycoumarin to a furocoumarin are given only once, using the synthesis of 4,5′-dimethylisopsoralene as an example. Other compounds listed were prepared by similar methods, with the exceptions noted.

All melting points in this section are corrected. Microanalyses and spectra analyses were carried out by Drs. Weiler and Strauss, Oxford University, England. Because Pathak and Fellman have demonstrated[20] a relationship between the wave length of light absorption and photosensitizing ability, the ultraviolet maximas and minimas of each furocoumarin are given.

Claisen rearrangement. 8Allyl-7-hydroxy-4-methylcoumarin (IV, R = CH_3). Forty-eight g. (0.22 mole) of 7-allyloxy-4-methylcoumarin (III, R = CH_3)[12a] were heated at 215–220° (temperature of reaction mixture) for 2 hr. in a closed vessel. The dark brown mass was dissolved in boiling ethanol, and decolorizing charcoal (*ca.* 5 g.) was added. The hot, filtered ethanol solution was diluted with excess water and a pale yellow precipitate of crude 8-allyl-7-hydroxy-4-methylcoumarin was collected. It weighed, after drying, 45.10 g. (94% yield, m.p. 172–186°) and was suitable for use in the next step, but filtration of an acetone solution through an activated charcoal column, followed by crystallization from ethanol, gave colorless needles, m.p. 198–199° (reported,[12a] m.p. 193–194°). This compound showed a blue fluorescence in aqueous alkali or in concd. sulfuric acid, but a warm ethanol solution gave no color with ferric chloride.

Acetylation. 7-Acetoxy-8-allyl-4-methylcoumarin (V, R = CH_3). A mixture of 45.10 g. (0.175 mole) of crude 8-allyl-7-hydroxy-4-methylcoumarin and a few crystals of fused sodium acetate in 350 ml. of acetic anhydride was heated under reflux for 5 hr. and stirred with water until excess acetic anhydride had decomposed. An insoluble solid was collected by filtration and, after two recrystallizations from methanol, 40.00 g. (74% yield) of colorless needles, m.p. 87–87.5°, were obtained.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.8; H, 5.5. Found: C, 69.8; H, 5.5.

Bromination. 7-Acetoxy-8-(2′,3′-dibromopropyl)-4-methylcoumarin (VI, R = CH_3). A solution of 16.00 g. (0.1 mole)

(17) L. Claisen, *Ann.*, **418**, 72 (1918).

(18) C. D. Hurd, H. Greengard, and F. D. Pilgrim, *J. Am. Chem. Soc.*, **52**, 1700 (1930).

(19) R. Aneja, S. K. Mukerjee, and T. R. Seshadri, *Tetrahedron*, **4**, 256 (1958).

(20) M. A. Pathak and J. H. Fellman, *Nature*, **185**, 382 (1960).

of bromine in 100 ml. of glacial acetic acid was added dropwise to a well stirred solution of 25.80 g. (0.1 mole) of 7-acetoxy-8-allyl-4-methylcoumarin in 200 ml. glacial acetic acid kept at room temperature. The reaction mixture was diluted with water (*ca.* 1 l.) and the yellow tar, which appeared initially, solidified after standing for an hour. A solid (39.50 g., 95% yield, m.p. 148–152°) was collected by filtration and was satisfactory for use in the next step. Three crystallizations from ethanol gave pale yellow prisms, m.p. 156–157°.

Anal. Calcd. for $C_{15}H_{14}O_4Br_2$: C, 43.1; H, 3.4; Br, 38.2. Found: C, 43.1; H, 3.4; Br, 37.9.

Cyclization. 4,5'-Dimethylisopsoralene (VII, R = CH_3). A solution of 30.00 g. (0.0718 mole) of crude 7-acetoxy-8-(2',3'-dibromopropyl)-4-methylcoumarin and 40.30 g. (0.718 mole) of potassium hydroxide in 1 l. of 95% ethanol was heated under reflux for 2 hr. and concentrated to about one third of its original volume. Water (1.5 l.) was added and the solution was immediately acidified with dilute hydrochloric acid. The next day, a light brown solid was collected by filtration and washed with 5% aqueous ammonia (400 ml.). A chloroform solution of the dried solid was filtered through an activated charcoal column and evaporated to leave a residue which crystallized from 95% ethanol as 9.20 g. (60% yield) of colorless prisms, m.p. 182–183°. Light absorption in methanol: λ_{max} 2500, 2975, log ϵ 4.27, 3.93; λ_{min} 2300, 2750, log ϵ 3.95, 3.66.

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.9; H, 4.7. Found: C, 72.7; H, 4.8.

8-Allyl-7-hydroxycoumarin (IV, R = H). Seven g. (78% yield) of crude product, m.p. 144–155° and suitable for use in the next step, was obtained by Claisen rearrangement of 9.00 g. of 7-allyloxycoumarin (III, R = H)[12b] under the conditions described above. Recrystallization from ethanol gave colorless prisms, m.p. 165–166° (reported,[12b] 162–163°).

7-Acetoxy-8-allylcoumarin (V, R = H). Acetylation of 6.00 g. of crude 8-allyl-7-hydroxycoumarin gave, after crystallization from ligroin (b.p. 60–80°), 5.80 g. (80% yield) of colorless prisms, m.p. 93–93.5°.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.8; H, 5.0. Found: C, 69.2; H, 5.1.

7-Acetoxy-8-(2',3'-dibromopropyl)coumarin (VI, R = H). 7-Acetoxy-8-allylcoumarin (2.55 g., 0.0104 mole) and 1.67 g. (0.0104 mole) of bromine, under the conditions described above, gave 4.22 g. (quantitative yield) of crude dibromide, suitable for use in the next step. Colorless, felted needles crystallized from methanol, m.p. 123–123.5°.

Anal. Calcd. for $C_{14}H_{12}O_4Br_2$: C, 41.6; H, 3.0; Br, 39.5. Found: C, 41.7; H, 3.2; Br, 39.5.

5'-Methylisopsoralene (VII, R = H). Cyclization of 2.65 g. of crude 7-acetoxy-8-(2',3'-dibromopropyl)coumarin proceeded as described above, except that filtration through a charcoal column was unnecessary. Colorless needles (0.67 g., 51% yield) crystallized from methanol, m.p. 153–154°. Light absorption in methanol: λ_{max} 2500, 3000, log ϵ 4.36, 4.09; λ_{min} 2300, 2700, log ϵ 4.07, 3.71.

Anal. Calcd. for $C_{12}H_8O_3$: C, 72.0; H, 4.0. Found: C, 72.0; H, 3.9.

7-Hydroxy-8-methylcoumarin-3-carboxylic acid (IX, R = COOH). A mixture of 15.20 g. of 4-formyl-2-methylresorcinol (VIII),[15] 20.80 g. of malonic acid, and 2 ml. of aniline (distilled from zinc dust) in 80 ml. of pyridine was kept at 40–45° for 48 hr., acidified with 5% hydrochloric acid, and diluted with an excess of water. After dissolving the resultant precipitate in 5% aqueous sodium hydroxide and reprecipitating with hydrochloric acid, 20.14 g. (92% yield) of crude product, m.p. 254–255°, were obtained. Although the crude material was suitable for use in the next step, a small portion crystallized from glacial acetic acid, m.p. 258–259° dec.

Anal. Calcd. for $C_{11}H_8O_5$: C, 60.0; H, 3.7. Found: C, 59.9; H, 3.9.

7-Hydroxy-8-methylcoumarin (IX, R = H). A solution of 9.60 g. of crude 7-hydroxy-8-methylcoumarin-3-carboxylic acid in 100 ml. of freshly distilled glycerin was heated under reflux for 1 hr. and poured into 1 l. of water. The crude product (6.55 g., 85% yield) precipitated and was suitable for use in the next step. A small portion crystallized from ethanol as colorless needles, m.p. 258–259° (reported,[14] m.p. 231–232°). A mixture of this substance with the starting material had m.p. 237–253°.

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.2; H, 4.6. Found: C, 68.4; H, 4.7.

7-Allyloxy-8-methylcoumarin (X, R = H). A mixture of 6.55 g. of crude 7-hydroxy-8-methylcoumarin, 23.50 g. of anhydrous potassium carbonate, 16.8 ml. of allyl bromide, and 500 ml. of acetone was heated under reflux for 16 hr. and was then concentrated to dryness on a steam bath. Extraction of the powdered residue with 500 ml. of 5% aqueous ammonia, followed by crystallization from aqueous ethanol, gave 6.95 g. (87% yield) of off-white needles, m.p. 125–125.5°.

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.2; H, 5.6. Found: C, 72.5; H, 5.8.

6-Allyl-7-hydroxy-8-methylcoumarin (XI, R = H). Claisen rearrangement of 5.58 g. of 7-allyloxy-8-methylcoumarin, heated for 75 min. instead of 2 hr., gave 4.46 g. (80% yield) of crude product, suitable for use in the next step. Two recrystallizations from ethanol gave microcrystalline needles, m.p. 153–154°.

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.2; H, 5.6. Found: C, 71.9; H, 5.7.

7-Acetoxy-6-allyl-8-methylcoumarin. Acetylation of 3.70 g. of 6-allyl-7-hydroxy-8-methylcoumarin gave 3.53 g. (80% yield) of off-white prisms, m.p. 119–119.5° after crystallization from ethanol (charcoal).

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.8; H, 5.5. Found: C, 70.1; H, 5.5.

7-Acetoxy-6-(2',3'-dibromopropyl)-8-methylcoumarin. Bromination of 3.53 g. (0.0137 mole) of 7-acetoxy-6-allyl-8-methylcoumarin with 2.20 g. (0.0137 mole) of bromine gave 5.74 g. (quantitative yield) of crude dibromide, suitable for use in the next step. Pale yellow prisms, m.p. 129–130°, were obtained by two recrystallizations from ethanol.

Anal. Calcd. for $C_{15}H_{14}O_4Br_2$: C, 43.1; H, 3.4; Br, 38.2. Found: C, 43.4; H, 3.2; Br, 37.9.

5',8-Dimethylpsoralene (XII, R = H). Cyclization of 4.53 g. of crude 7-acetoxy-6-(2',3'-dibromopropyl)-8-methylcoumarin was achieved in a manner analogous to the procedure described above. Crystallization from methanol gave 1.13 g. (49% yield) of colorless prisms, m.p. 176–177°. Light absorption in methanol: λ_{max} 2500, 3000, 3350, log ϵ 4.39, 4.12, 3.83; λ_{min} 2300, 2700, 3300, log ϵ 4.20, 3.77, 3,82.

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.9; H, 4.7. Found: C, 72.8; H, 4.9.

7-Acetoxy-6-allyl-4,8-dimethylcoumarin. 7-Allyloxy-4,8-dimethylcoumarin[13] (195.0 g.) underwent Claisen rearrangement under the conditions described above, except that the crude 6-allyl-7-hydroxy-4,8-dimethylcoumarin obtained was only partially dry after heating at 70° for 6 hr. The moist solid was acetylated (915 ml. of acetic anhydride) to give 145.4 g. (64% yield for the two steps) of colorless needles, m.p. 144.5–145.5°, after recrystallization from ethanol.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.6; H, 5.9. Found: C, 70.6; H, 5.9.

7-Acetoxy-6-(2',3'-dibromopropyl)-4,8-dimethylcoumarin. Because of the larger quantities involved, bromination was carried out in chloroform rather than acetic acid. A solution of 85.2 g. (0.534 mole) of bromine in 200 ml. of chloroform was added to a chilled (ice bath) solution of 145.4 g. (0.534 mole) of 7-acetoxy-6-allyl-4,8-dimethylcoumarin in 800 ml. of chloroform at such a rate as to keep the temperature below 25°. Evaporation of chloroform on the steam bath left an off-white residue weighing 230.6 g. (quantitative yield) which was suitable for use in the next step. Crystal-

lization of a small portion from ethanol gave colorless prisms, m.p. 141.5–142.5°.

Anal. Calcd. for $C_{16}H_{16}O_4Br_2$: C, 44.5; H, 3.7; Br, 37.0. Found: C, 44.7; H, 4.1; Br, 36.9.

4,5',8-Trimethylpsoralene (XII, R = CH_3). Crude 7-acetoxy-6-(2',3'-dibromopropyl)-4,8-dimethylcoumarin (245.7 g., 0.57 mole) was heated under reflux for 1.75 hr. in a solution of 65.4 g. (2.85 mole) of sodium in 2.1 l. of absolute ethanol (magnesium dried). After cooling for 15 min., the reaction mixture was poured into a mixture of 8 kg. of ice and 8 l. of 3.5% hydrochloric acid. The precipitate obtained was washed with 5% aqueous sodium hydroxide followed by water, and dried in a vacuum desiccator. Fractional crystallization from chloroform–petroleum ether (b.p. 30–60°) using Norit and finally from chloroform alone gave 61.8 g. (48% yield) of colorless prisms, m.p. 234.5–235°. Light absorption in methanol: λ_{max} 2500, 2950, 3350, log ϵ 4.35, 3.99, 3.80; λ_{min} 2250, 2700, 3200, log ϵ 4.09, 3.68, 3.79.

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.7; H, 5.3. Found: C, 73.4; H, 5.4.

3-Allyloxyphenyl acetate (XIV). A mixture of 101.3 g. of resorcinyl monoacetate, 138.2 g. of anhydrous potassium carbonate, and 181.5 g. of allyl bromide in 300 ml. of acetone was heated under reflux for 24 hr. and concentrated to dryness on a steam bath. Water (1.5 l.) was added and an ethereal extract of the aqueous solution was washed with 5% aqueous ammonia, dried (magnesium sulfate), and concentrated to an oil which gave, on distillation, 105.5 g. (82% yield) of a colorless oil, b.p. 82°/0.05 mm. This sample gave a faint red-brown ferric chloride color in ethanol.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.8; H, 6.4; active H, 0.0. Found: C, 69.1; H, 6.4; active H, 0.13.

Mixture of 2-allyl- and 4-allylresorcinol (XV and XVI). A solution of 60.2 g. of 3-allyloxyphenyl acetate in 100 ml. of diethylaniline was heated under reflux (nitrogen atmosphere) for 50 min., dissolved in ether, and thoroughly washed with 5% hydrochloric acid. Extraction with 5% aqueous sodium hydroxide gave an oil, on acidification of the alkaline extract, which was isolated with ether and distilled through a short Vigreux column. A pale yellow oil (34.2 g., 73% yield), b.p. 98°/0.1 mm.; n_D^{17} 1.5630, was obtained and a small sample gave an intense red-brown color with ferric chloride in ethanol.

Anal. Calcd. for $C_9H_{10}O_2$: C, 72.0; H, 6.7; active H, 1.34. Found: C, 71.9; H, 7.0; active H, 1.30.

Condensation of mixed allylresorcinols with ethyl acetoacetate. A solution of 5.00 g. of the mixture (described above) in 50 ml. of glacial acetic acid containing 4.33 g. of ethyl acetoacetate was saturated with dry hydrogen chloride. The next day, the reaction mixture was poured into water and the oil, which separated initially, solidified after several days. An ether solution of the solid was extracted with 5% aqueous ammonia and acidification of the ammonia extract gave a solid which crystallized from aqueous ethanol as 4.07 g. of colorless prisms, m.p. 137–160°. Repeated crystallizations from ethanol gave 0.035 g. of colorless needles of 8-allyl-7-hydroxy-4-methylcoumarin (IV, R = CH_3), m.p. 198–199° alone or mixed with the specimen prepared by Claisen rearrangement. The infrared spectra of the two specimens were identical. The recrystallization mother liquors were diluted with water and 4.01 g. of a white solid were obtained.

7-Acetoxy-6-allyl-4-methylcoumarin. Acetylation of 1.151 g. of the above white solid, with sodium acetate and acetic anhydride, gave 1.125 g. of colorless needles, m.p. 85–110°, after crystallization from ethanol. This material (0.70 g.) in benzene, was adsorbed on a column of acid-washed alumina. A small portion of a 50% chloroform-benzene mixture eluted 0.050 g. of a white solid, which crystallized from ethanol as colorless needles, m.p. 135–136°.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.8; H, 5.5. Found: C, 69.6; H, 5.1.

6-Allyl-7-hydroxy-4-methylcoumarin (XVII). Further elution of the above alumina column with 50% chloroform-benzene gave 0.25 g. of 8-allyl-7-hydroxy-4-methylcoumarin (IV, R = CH_3). Finally, chloroform eluted from the column 0.23 g. of a solid, which crystallized from ethanol as colorless needles, m.p. 174–175°, of 6-allyl-7-hydroxy-4-methylcoumarin (XVII).

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.2; H, 5.6. Found: C, 72.2; H, 5.6.

Acetylation with sodium acetate and acetic anhydride gave a sample of 7-acetoxy-6-allyl-4-methylcoumarin, which was identical (mixed melting point) with the sample described above.

7-Acetoxy-6-(2',3'-dibromopropyl)-4-methylcoumarin. Bromination of 0.119 g. of 7-acetoxy-6-allyl-4-methylcoumarin in glacial acetic acid gave 0.191 g. (quantitative yield) of crude dibromide, suitable for use in the next step. A small portion crystallized from ethanol as pale yellow prisms, m.p. 150–151°.

Anal. Calcd. for $C_{15}H_{14}O_4Br_2$: C, 43.1; H, 3.4; Br, 38.2. Found: C, 43.5; H, 3.4; Br, 38.1.

4,5'-Dimethylpsoralene (XVIII). Cyclization of 0.155 g. of crude 7-acetoxy-6-(2',3'-dibromopropyl)-4-methylcoumarin was accomplished by the use of ethanolic potassium hydroxide. The product crystallized from ethanol as 0.044 g. (55% yield) of colorless needles, m.p. 161–162°. Light absorption in methanol: λ_{max} 2450, 2900, 3400, log ϵ 4.28, 3.82, 3.68; λ_{min} 2700, 3100, log ϵ 3.56, 3.61.

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.9; H, 4.7. Found: C, 73.0; H, 4.7.

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