Synthesis of 4,7,9-Trimethyl-2*H*-thieno[3,2-*g*]-1-benzopyran-2-one. A Psoralen Isostere

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The title compound, an isostere of 4,5',8-trimethylpsoralen, was prepared in good yield from 7-[(2-bromoallyl)thio]-4,8-dimethylcoumarin *via* a thio-Claisen rearrangement. The structure of the final product was determined by proton nmr decoupling experiments.

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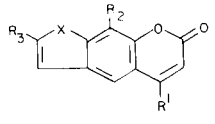
The psoralens are a class of potent dermal sensitizing agents that promote sun tanning and have been used clinically in the treatment of vitiligo (2). Great interest has been stimulated recently by the discovery that psoralens can be used effectively in the treatment of psoriasis (3,4). Of the two agents used clinically in the United States (2), trioxsalen **1** (5) is both more potent and less toxic than methoxsalen **2** (6). While a great many psoralen derivatives are known, there are none reported which contain a ring sulfur atom. This paper describes the synthesis of the title compound, the first reported example of its kind, utilizing an unusual thio-Claisen rearrangement as a key step. While the generality of this synthesis has not been established, the ease of the described synthesis of the title compound suggests this is a good route to 2-methylbenzothiophenes in general.



Compound No.	X	R_1	R_2	R_3
1	O	CH_3	CH_3	CH_3
2	O	H	OCH_3	H
3	S	CH_3	CH_3	CH_3

Kaufman reported the synthesis of **1** in 1961 (7). His route to methyl psoralens utilized a Claisen rearrangement of 7-allyloxycoumarins to give 6-allyl-7-hydroxycoumarins. These were brominated and treated with base to effect cyclization to the psoralens. Subsequently, it was found by Kaufman and Hewitt that 7-(2-bromoallyloxy)-coumarins could be rearranged directly to psoralens although the intermediate 6-(2-bromoallyl)-7-hydroxycoumarin could be isolated if desired (8).

Thus it appeared that **3** could be prepared by an analogous route providing that the proper sulfur analog **8** could be induced to undergo a thio-Claisen rearrangement followed by the requisite addition and dehydrohalogenation. Thio-Claisen rearrangements appear to run smoothly when done in basic solvents such as quinoline (9). Kwart and co-workers have reported, however, that the products, allyl phenyl sulfides, generally react further yielding thiachroman (6 membered sulfur ring) and 2-methythiacoumarans (5 membered sulfur ring) (9). Interestingly, Kwart and Cohen reported that β-chloro-allylphenyl sulfide underwent a thio-Claisen rearrangement followed by further reaction to give 2-methylbenzo[*b*]thiophene (10). The reported yield for this reaction was only 41% however, and the nature of the other products was not reported.

Based on the work of Kaufman and Hewitt and that of Kwart and Cohen, it appeared that 7-(2-bromoallylthio)-coumarin **8** might be converted directly to **3**. The synthesis of **8** was readily achieved starting with 4,8-dimethyl-7-hydroxycoumarin. The coumarin **4** was treated with base and dimethylthiocarbamoyl chloride yielding the thiocarbamate ester **5** (11). This was thermally rearranged to **6** and hydrolyzed to yield the thiol **7**. Reaction of **7** with commercially available 2,3-dibromopropene gave **8** in good yield.

The thio-Claisen rearrangement of **8** was carried out in dimethyl aniline heated under reflux for 48 hours. The reaction was relatively slow, the starting thio-ether **8** still being detectable by tlc after 67 hours. There was no apparent build-up of intermediates during the reaction suggesting that the thio-Claisen rearrangement was the slowest step. The reaction was fairly clean and while minor products were detectable in the reaction mixture by tlc, the desired product **3** was easily isolated in 67% yield and an additional 9% of **3** could be isolated by column chromatography.

Analysis of the product by nmr showed that it clearly had the desired structure shown for **3** as opposed to a six membered sulfur ring structured compound such as **9**. There are three methyl resonances and three resonances in the aromatic region and two of the methyl groups (and two of the aromatic protons) exhibited long range coupling of about 0.6 Hz.

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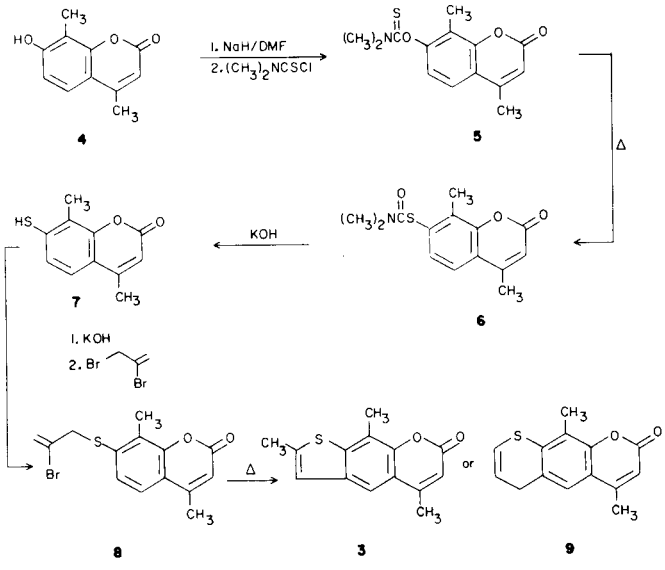

Evaluation of the sunsensitizing activity of the title compound suggests that it is not as potent as the related psoralens **1** and **2**. Further biological evaluation is in progress.

Acknowledgement.

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EXPERIMENTAL

General.

The ^1H nmr spectra were obtained on a Perkin Elmer spectrometer using deuteriochloroform as solvent and tetramethylsilane as an internal standard. Melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were carried out by Galbraith, Nashville, Tenn.

Preparation of 7-Hydroxy-4,8-dimethylcoumarin Dimethylthiocarbamate (**5**).

4,8-Dimethyl-7-hydroxycoumarin (**4**) (37 g., 0.195 mole) was dissolved in 400 ml. of dry dimethylformamide. The solution was stirred and sodium hydride was added (9 g. of a 57% oil dispersion, 0.234 mole). Stirring was continued until the evolution of hydrogen had ceased. Dimethylthiocarbamoyl chloride (25 g., 0.2 mole) was added in one portion and the solution heated to 60° for 30 minutes. The solution, which begins to deposit crystals if cooled slightly, was poured into 2 l. of cold water. The crude precipitated product weighed 45 g. after drying and was recrystallized from ethanol yielding 38 g. (70%) of **5** in three crops. An analytical sample was prepared by multiple recrystallization from ethanol and had a m.p. 230-232°.

Anal. Calcd. for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.44. Found: C, 60.60; H, 5.36.

Preparation of 7-Mercapto-4,8-dimethylcoumarin Dimethylcarbamate (**6**).

7-Hydroxy-4,8-dimethylcoumarin dimethylthiocarbamate (**5**) (7.7 g., 0.028 mole) was heated neat under nitrogen to 240-250° for 40 minutes using an oil bath. The melt was cooled and crystallized from ethanol in two crops yielding 7.1 g. (93%), m.p. 219-221°. An analytical sample was prepared by recrystallization from ethanol using Norit to give a sample of **6** with a m.p. 220-222°.

Anal. Calcd. for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.44. Found: C, 60.60; H, 5.36.

Preparation of 7-Mercapto-4,8 dimethylcoumarin (**7**).

7-Hydroxy-4,8-dimethylcoumarin dimethylcarbamate (**6**) (25 g., 0.09 mole) was rearranged as indicated for the preparation of **6**. The solid product without purification was heated under reflux with 1 l. of methanol containing potassium hydroxide (5.05 g., 0.09 mole) and the solution concentrated to 700 ml. after 8 hours by distillation. The solution was acidified with concentrated hydrochloric acid and water, about 100 ml., added to cause opalecence. The solution was cooled to 10° and deposited 17.2 g. (93%) of **7**, m.p. 147-148°. An analytical sample was obtained by recrystallization from 1:10 ethanol-cyclohexane and yielded a product with a m.p. 145-146°.

Anal. Calcd. for $C_{11}H_{10}O_2S$: C, 64.05; H, 4.89. Found: C, 64.10; H, 4.88.

Preparation of 7-[(2-Bromoallyl)thio]-4,8-dimethylcoumarin (**8**).

7-Mercapto-4,8-dimethylcoumarin (**7**), (15 g., 0.074 mole), was dissolved in 500 ml. of methanol and potassium hydroxide (5 g., 0.09 mole) cautiously dissolved in this solution. The solution was stirred and 2,3-dibromo-1-propene (9 ml.) added in one portion. The solution was heated under reflux for 1 hour and concentrated to 400 ml. The solution was acidified with concentrated hydrochloric acid and diluted with 75 ml. of water. The solution deposited 21.0 g. (88%) of **8**, m.p. 110-114°. An analytical sample was obtained by recrystallization from cyclohexane giving **8** with a m.p. 114-115°.

Anal. Calcd. for $C_{14}H_{13}BrO_2S$: C, 51.70; H, 4.03. Found: C, 51.78; H, 3.98.

Preparation of 4,7,9-Trimethyl-2*H*-thieno[3,2-*g*]-1-benzopyran-2-one (**3**).

7-[(2-Bromoallyl)thio]-4,8-dimethylcoumarin (**8**) (5 g., 0.0154 mole) was heated under reflux in freshly distilled dimethylaniline under a nitrogen blanket for 48 hours. The solution was cooled and poured into 150 ml. of chloroform and extracted with 10% hydrochloric acid (2 × 200 ml.) and water (2 × 150 ml.) and finally dried over sodium carbonate. The chloroform was then removed under vacuum distillation and the residue crystallized from 200 ml. of ethanol. The solution deposited 2.5 g. (67%) of **3**, m.p. 200-208°. The crystallization mother liquor was concentrated and chromatographed over silica gel eluting with methylene chloride-cyclohexane 2:1. From the column was obtained an additional 350 mg. (9%). An analytical sample was obtained by recrystallization from benzene using Norit and finally from ethyl acetate, m.p. 208-211°; nmr: δ 2.41 (d, 3, J = 0.6 Hz, 4-CH_3), 2.48 (s, 3, 9-CH_3), 2.56 (d, 3, J = 0.6 Hz, 7-CH_3), 6.18 (d, 1, J = 0.6 Hz, 3-H), 6.95 (d, 1, J = 0.6 Hz, 6-H), 7.60 (s, 1, 4-H). Irradiation of the signals at δ 6.18 and 6.95 caused the collapse of the signals at δ 2.41 and 2.56, respectively.

Anal. Calcd. for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95; S, 13.12. Found: C, 68.71; H, 4.95; S, 13.14.

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