Synthesis of Methyl Derivatives of Linear and Angular Thienocoumarins and Thiopyranocoumarins

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New linear and angular thienocoumarins and thiopyranocoumarins were synthesized. The key intermediates were appropriate methyl derivatives of 7-mercaptocoumarin, which were condensed with chloroketones or propargyl chloride. Thioethers were cyclized under various conditions in order to determine which methods produced the best yields of the desired thienocoumarins **15**, **16**, **17**, **18**, **22**, **23**, **24**, **27** and thiopyranocoumarins **28** and **29**.

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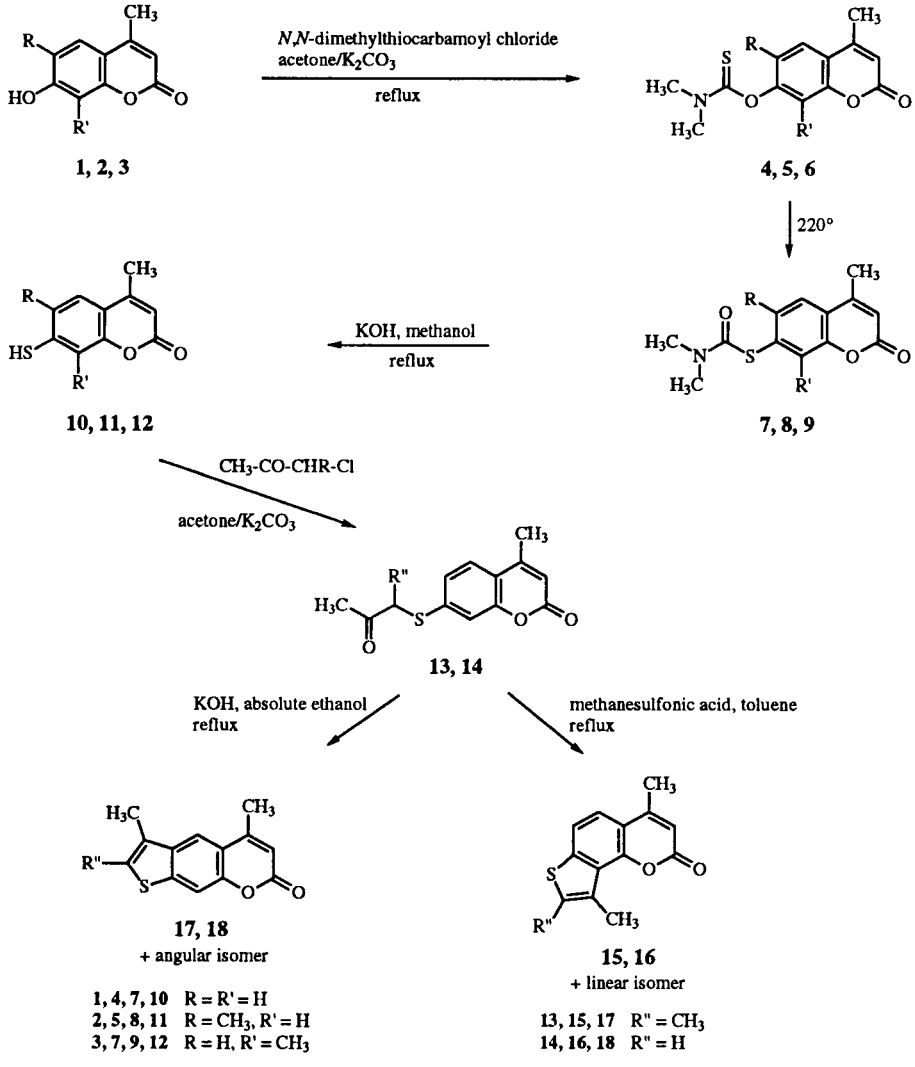
Furocoumarins are a class of compounds known for their photobiological activity [1]. Some psoralens, linear furocoumarins, are commonly used in psoralen photochemotherapy [2] to treat various skin diseases and

Scheme 1



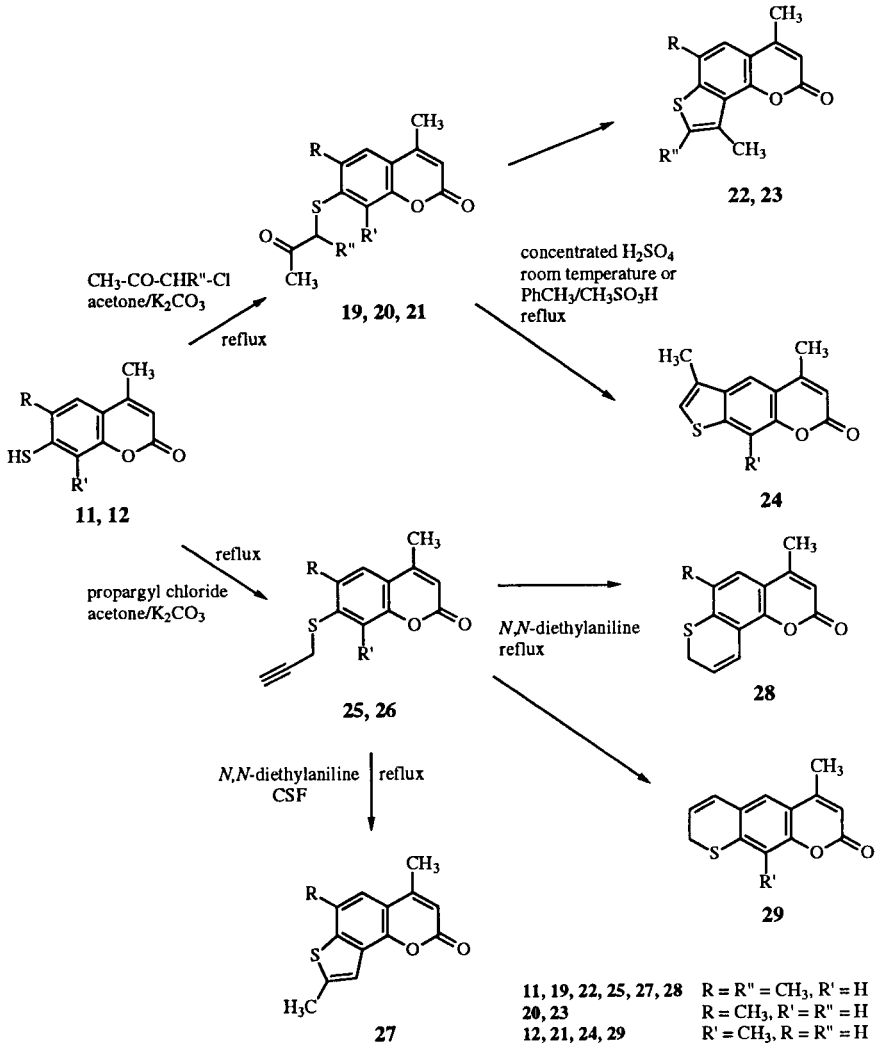
more recently in photopheresis [3]. Their mechanism of action is correlated with their capacity to intercalate in DNA and to photolink when irradiated with uv light [4]. With the aim of eliminating some undesirable side-effects (genotoxicity and phototoxicity), attributed to their capacity to cross-link with the macromolecule of DNA, a new series of tetracyclic compounds [5] and various isosters of psoralen and angelicin were prepared [6,7,8]. Unexpectedly, some structures showed antiproliferative activity in the dark, connected with topoisomerase II inhibition [7,9]. In addition, the synthesis of 4,8-dimethyl-2*H*-thieno[2,3-*h*]-1-benzopyran-2-one [10] and recently of psoralen, with sulfur or selenium atoms replacing oxygen atoms but lacking in methyl groups, has been described [11].

Continuing our work on new antiproliferative compounds, this paper describes the synthesis of new methyl derivatives of angular and linear thienocoumarins and thiopyranocoumarins.

Synthesis of thienocoumarins started from methyl derivatives of 7-hydroxy-4-methylcoumarin **1** which, having positions 6 and 8 free, gave rise to linear and angular thienocoumarins. In the synthesis of furocoumarins, alkaline and acidic conditions were regioselective, but in that of thienocoumarins the same reaction gave rise to a mixture of two isomers. Therefore, in order to avoid the presence of linear isomers in the angular derivatives and of angular isomers in the linear compounds, we started from 6-methyl-7-hydroxycoumarin or 8-methyl-7-hydroxycoumarin which, under all conditions used, always yielded the desired tricyclic compounds.

In synthesising thienocoumarins, it is essential to introduce the sulfur-containing group into the coumarin moiety at position 7. In order to substitute the phenolic hydroxyl group with a mercapto group, suitable 7-hydroxycoumarins **1**, **2**, **3** were condensed with *N*,*N*-dimethylthiocarbamoyl chloride in acetone solution in the presence of potassium carbonate (Scheme 1). Later heating in a ther-

Scheme 2



mostatic bath (10 degrees up to melting point) under a constant flux of nitrogen yielded the isomerization of *N,N*-dimethylthiocarbamates **4**, **5**, **6** to *N,N*-dimethylcarbamates **7**, **8**, **9** [12]. The hydrolysis of **7**, **8** and **9** in an alkaline medium yielded the key compounds 7-mercapto-4-methyl- **10**, 7-mercapto-4,6-dimethyl- **11** and 7-mercapto-4,8-dimethylcoumarin **12**. Various strategies were followed to identify the best way of condensing the thiophene ring onto the coumarin.

In the first method (Scheme I), 7-mercapto-4-methylcoumarin (**10**) was condensed with two chloroketones, producing the corresponding thioethers **13** and **14** which, when cyclized, mainly yielded 4,8,9-trimethyl-2*H*-thieno[2,3-*h*]-1-benzopyran-2-one (**15**) and 4,9-dimethyl-2*H*-thieno[2,3-*h*]-1-benzopyran-2-one (**16**) under acidic conditions, and 4,6,7-trimethyl-2*H*-thieno[3,2-*g*]-1-benzopyran-2-one (**17**) and 4,6-dimethyl-2*H*-thieno[3,2-*g*]-1-benzopyran-2-one (**18**) under alkaline conditions. Fractional crystallization only provided partial purification, as shown by hplc analysis, and this precluded the use of the final product in an experimental biological context, because the activities of linear and angular compounds are very different.

Therefore, as previously reported, we synthesized thienocoumarin derivatives starting from a coumarin with a methyl group in positions 6 or 8. Consequently, 7-mercapto-4,6-dimethylcoumarin (**11**), obtained from 7-hydroxy-4,6-dimethylcoumarin (**2**), was condensed with chloroacetone and 3-chlorobutan-2-one (Scheme 2). Thioethers **19** and **20**, upon cyclization in acidic medium, yielded 4,6,8,9-tetramethyl-2*H*-thieno[2,3-*h*]-1-benzopyran-2-one (**22**) and 4,6,9-trimethyl-2*H*-thieno[2,3-*h*]-1-benzopyran-2-one (**23**) respectively. Cyclization under acidic conditions was preferred, in order to avoid the partial hydrolysis which occurs under alkaline conditions.

In a similar manner, starting from 4,8-dimethyl-7-mercaptocoumarin (**12**) acetonyl ether **21** was obtained, which upon cyclization yielded 4,6,9-trimethyl-2*H*-thieno[3,2-*g*]-1-benzopyran-2-one (**24**).

Alternatively (Scheme 2), 7-mercaptocoumarin **11** was condensed with propargyl chloride, yielding thioether **25**, which was cyclized upon boiling in diethylaniline in the presence of cesium fluoride as the catalyst. Under these conditions, thienocoumarin **27** with a methyl group in position 5' of the furan ring was obtained, but with a small yield.

For the synthesis of thiopyranocoumarins, propargyl derivatives **25** and **26** were cyclized by boiling them in diethylaniline providing thiopyranocoumarins **28** and **29**. Linear cyclization was complete upon refluxing the reaction mixture for 15 hours, owing to a minor activation of the 6-position of the coumarin. In addition, trace amounts of a partial decomposition of the starting material were observed.

EXPERIMENTAL

General Methods

Melting points (uncorrected) were determined using a Gallenkamp MFB-595-010M melting point apparatus. Analytical thin-layer chromatography (tlc) was performed on pre-coated silica gel plates 60 F_{254} (Merck, 0.2 mm), developing with an ethyl acetate-cyclohexane mixture (3:7). Preparative column chromatography was performed using silica gel 60 (Merck, 0.063-0.100 mm) eluting with chloroform. The ^{1}H nmr spectra were recorded on a Varian Gemini 200-MHz spectrometer. The hplc were performed using a Perkin-Elmer Series 410, equipped with LCI 100 Laboratory Computing Integrator and LC Array Detector; column LiChrosorb RP-18, 5 μm, 10 cm, Φ = 1 ml/minute, eluting with a gradient methanol/water: 2 minutes methanol 60%, 10 minutes (linear gradient) methanol 60-80%, 5 minutes methanol 80%, 1 minute (linear gradient) methanol 80-100%, 10 minutes methanol 100%. Elemental analyses were carried out by the Microanalytical Laboratory of the Department of Pharmaceutical Sciences of the University of Padova, under the direction of M. Zancato.

7-(4-Methylcoumarinyl)-*N,N*-dimethylthiocarbamate (**4**).

To a solution of 7-hydroxy-4-methylcoumarin (**1**) (6.7 g, 38.1 mmoles) in acetone (800 ml) *N,N*-dimethylthiocarbamoyl chloride (9.3 g, 75.2 mmoles) and anhydrous potassium carbonate (20.0 g) were added and the mixture was refluxed until the starting material disappeared (18 hours, tlc). After cooling, potassium carbonate was filtered and washed with fresh acetone. The solvent was evaporated from the pooled filtrate, and washings yielding a solid which was crystallized from ethyl acetate to give 7.9 g (79%) of 7-(4-methylcoumarinyl)-*N,N*-dimethylthiocarbamate (**4**), mp 211°; ^{1}H nmr (deuteriochloroform): δ 7.62 (d, J = 9.3 Hz, 1 H, H-5), 7.07 (d, J = 2.2 Hz, 1 H, H-8), 7.07 (dd, J = 9.3 Hz, J = 2.2 Hz, 1 H, H-6), 6.28 (q, J = 1.2 Hz, 1 H, H-3), 3.47 (s, 3 H, Me-N), 3.38 (s, 3 H, Me-N), 2.44 (d, J = 1.2 Hz, 3 H, Me-4).

Anal. Calcd. for $C_{13}H_{13}NO_3S$ (263.3): C, 59.30; H, 4.98; N, 5.32; S, 12.18. Found: C, 59.16; H, 4.86; N, 5.09; S, 12.06.

7-(4,6-Dimethylcoumarinyl)-*N,N*-dimethylthiocarbamate (**5**).

This compound was prepared from 7-hydroxy-4,6-dimethylcoumarin (**2**) in an analogous manner to **4**, mp 245° (methanol, 76%); ^{1}H nmr (deuteriochloroform): δ 7.44 (q, J = 0.8 Hz, 1 H, H-5), 7.01 (s, 1 H, H-8), 6.25 (q, J = 1.2 Hz, 1 H, H-3), 3.48 (s, 3 H, Me-N), 3.40 (s, 3 H, Me-N), 2.43 (d, J = 1.2 Hz, 3 H, Me-4), 2.27 (d, J = 0.8 Hz, 3 H, Me-6).

Anal. Calcd. for $C_{14}H_{15}NO_3S$ (277.3): C, 60.63; H, 5.45; N, 5.05; S, 11.56. Found: C, 60.49; H, 5.37; N, 5.01; S, 11.40.

7-(4,8-Dimethylcoumarinyl)-*N,N*-dimethylthiocarbamate (**6**).

This compound was prepared from 7-hydroxy-4-methylcoumarin (**3**) in an analogous manner to **4**, mp 230-231° (methanol, 73%): δ 7.49 (d, J = 8.5, 1 H, H-5), 7.00 (d, J = 8.5, 1 H, H-8), 6.28 (q, J = 1.2 Hz, 1 H, H-3), 3.49 (s, 3 H, Me-N), 3.09 (s, 3 H, Me-N), 2.44 (d, J = 1.2, 3 H, Me-4), 2.30 (broad s, 3 H, Me-8).

Anal. Calcd. for $C_{14}H_{15}NO_3S$ (277.3): C, 60.63; H, 5.45; N, 5.05; S, 11.56. Found: C, 60.39; H, 5.27; N, 4.93; S, 11.38.

7-(4-Methylcoumarinyl)mercapto-*N*,*N*-dimethylcarbamate (**7**).

7-(4-Methylcoumarinyl)-*N*,*N*-dimethylthiocarbamate (**4**) (7.0 g, 26.6 mmoles) was heated in a thermostatic bath at 220° under a flux of nitrogen until the starting material disappeared (2 hours). The crude mixture was crystallized from ethanol, giving 6.2 g (89%) of 7-(4-methylcoumarinyl)mercapto-*N*,*N*-dimethylcarbamate (**7**), mp 162°; ^{1}H nmr (deuteriochloroform): δ 7.60 (d, J = 8.3 Hz, 1 H, H-5), 7.49 (d, J = 1.6 Hz, 1 H, H-8), 7.43 (dd, J = 8.3 Hz, J = 1.6 Hz, 1 H, H-6), 6.32 (q, J = 1.2 Hz, 1 H, H-3), 3.07 (broad s, 6 H, Me-N), 2.44 (d, J = 1.2 Hz, 3 H, Me-4).

Anal. Calcd. for $C_{13}H_{13}NO_3S$ (263.3): C, 59.30; H, 4.98; N, 5.32; S, 12.18. Found: C, 59.21; H, 4.75; N, 5.29; S, 12.00.

7-(4,6-Dimethylcoumarinyl)mercapto-*N*,*N*-dimethylcarbamate (**8**).

This compound was prepared from 7-(4,6-dimethylcoumarinyl)-*N*,*N*-dimethylthiocarbamate (**5**) in an analogous manner to **7**, mp 206° (ethanol, 82%); ^{1}H nmr (deuteriochloroform): δ 7.50 (s, 1 H, H-5), 7.49 (s, 1 H, H-8), 6.30 (q, J = 1.2 Hz, 1 H, H-3), 3.09 (broad s, 6 H, Me-N), 2.47 (broad s, 3 H, Me-6), 2.42 (d, J = 1.2 Hz, 3 H, Me-4).

Anal. Calcd. for $C_{14}H_{15}NO_3S$ (277.3): C, 60.63; H, 5.45; N, 5.05; S, 11.56. Found: C, 60.51; H, 5.31; N, 4.96; S, 11.30.

7-(4,8-Dimethylcoumarinyl)mercapto-*N*,*N*-dimethylcarbamate (**9**).

This compound was prepared from 7-(4,8-dimethylcoumarinyl)-*N*,*N*-dimethylthiocarbamate (**6**) in an analogous manner to **7**, mp 225-226° (ethanol, 78%); ^{1}H nmr δ (deuteriochloroform): δ 7.45 (s, 2 H, H-5 and H-6), 6.32 (q, J = 1.2 Hz, 1 H, H-3), 3.14 (broad s, 3 H, Me-N), 3.04 (broad s, 3 H, Me-N), 2.55 (s, 3 H, Me-8), 2.43 (d, J = 1.2, 3 H, Me-4).

Anal. Calcd. for $C_{14}H_{15}NO_3S$ (277.3): C, 60.63; H, 5.45; N, 5.05; S, 11.56. Found: C, 60.43; H, 5.36; N, 4.88; S, 11.50.

7-Mercapto-4-methylcoumarin (**10**).

To a solution of 7-(4-methylcoumarinyl)mercapto-*N*,*N*-dimethylcarbamate (**7**) (6.1 g, 23.2 mmoles) in 1900 ml of methanol, a solution of potassium hydroxide (3.9 g, 69.5 mmoles) in 100 ml of methanol was added and the mixture was refluxed in the dark until the starting material disappeared (2 hours; tlc). The mixture was cooled and acidified with diluted hydrochloric acid. After elimination of methanol, the aqueous solution was extracted with ethyl acetate, the organic phase dried (anhydrous sodium sulfate) and the solvent eliminated under reduced pressure. The residue was crystallized from 2-propanol yielding 3.6 g (81%) of 7-mercapto-4-methylcoumarin (**10**), mp 137°; ^{1}H nmr (deuteriochloroform): δ 7.44 (d, J = 8.3 Hz, 1 H, H-5), 7.21 (d, J = 1.7 Hz, 1 H, H-8), 7.14 (dd, J = 8.3 Hz, J = 1.7 Hz, 1 H, H-6), 6.23 (q, J = 1.2 Hz, 1 H, H-3), 3.68 (s, 1 H, -SH), 2.40 (d, J = 1.2 Hz, 3 H, Me-4).

Anal. Calcd. for $C_{10}H_8O_2S$ (192.2): C, 62.48; H, 4.19; S, 16.68. Found: C, 62.40; H, 4.01; S, 16.40.

4,6-Dimethyl-7-mercaptocoumarin (**11**).

This compound was prepared from 7-(4,6-dimethylcoumarinyl)mercapto-*N*,*N*-dimethylcarbamate (**8**) in an analogous manner to **10**, mp 188° (ethyl acetate, 76%); ^{1}H nmr (deuteriochloroform): δ 7.33 (broad s, 1 H, H-5), 7.22 (s, 1 H, H-8), 6.21 (q, J = 1.2 Hz, 1 H, H-3), 3.60 (s, 1 H, -SH), 2.39 (d, J = 1.2 Hz, 3 H, Me-4), 2.37 (broad s, 3 H, Me-6).

Anal. Calcd. for $C_{11}H_{10}O_2S$ (206.3): C, 64.05; H, 4.89; S, 15.54. Found: C, 63.92; H, 4.79; S, 15.37.

4,8-Dimethyl-7-mercaptocoumarin (**12**).

This compound was prepared from 7-(4,8-dimethylcoumarinyl)mercapto-*N*,*N*-dimethylcarbamate (**9**) in an analogous manner to **10**, mp 146-147° (ethyl acetate, 79%); ^{1}H nmr (deuteriochloroform): δ 7.28 (d, J = 8.4, 1 H, H-5), 7.16 (d, J = 8.4, 1 H, H-6), 6.20 (q, J = 1.2 Hz, 1 H, H-3), 3.60 (s, 1 H, -SH), 2.40 (s, 3 H, Me-8), 2.39 (d, J = 1.2 Hz, 3 H, Me-4).

Anal. Calcd. for $C_{11}H_{10}O_2S$ (206.3): C, 64.05; H, 4.89; S, 15.54. Found: C, 63.89; H, 4.65; S, 15.39.

4-Methyl-7-(1'-methylacetonyl)mercaptocoumarin (**13**).

To a solution of 7-mercapto-4-methylcoumarin (**10**) (2.4 g, 12.4 mmoles) in 800 ml of acetone, 3-chlorobutan-2-one (1.3 g, 12.2 mmoles) and anhydrous potassium carbonate (70.0 g) were added and the mixture was refluxed until the fluorescent starting material disappeared (2 hours, tlc). After cooling, the potassium carbonate was filtered and washed with fresh acetone. The solvent was evaporated from the pooled filtrate and washings yielded a solid which was crystallized from ethyl acetate to give 2.3 g (72%) of 4-methyl-7-(1'-methylacetonyl)mercaptocoumarin (**13**), mp 107-108°; ^{1}H nmr (deuteriochloroform): δ 7.50 (d, J = 8.3 Hz, 1 H, H-5), 7.29 (d, J = 1.7 Hz, 1 H, H-8), 7.22 (dd, J = 8.3 Hz, J = 1.7 Hz, 1 H, H-6), 6.27 (q, J = 1.1, 1 H, H-3), 3.92 (q, J = 7.2 Hz, 1 H, H-1'), 2.42 (d, J = 1.1 Hz, 3 H, Me-4), 2.30 (s, 3 H, H-3'), 1.50 (d, J = 7.2 Hz, 3 H, Me-1').

Anal. Calcd. for $C_{14}H_{14}O_3S$ (262.3): C, 64.10; H, 5.38; S, 12.22. Found: C, 64.01; H, 5.23; S, 11.98.

7-Acetonylmercapto-4-methylcoumarin (**14**).

This compound was prepared from 7-mercapto-4-methylcoumarin (**10**), using chloroacetone, in an analogous manner to **13**, mp 135° (methanol, 73%); ^{1}H nmr (deuteriochloroform): δ 7.50 (d, J = 8.8, 1 H, H-5), 7.19 (d, J = 1.9 Hz, 1 H, H-8), 7.18 (dd, J = 8.8 Hz, J = 1.9 Hz, 1 H, H-6), 6.24 (q, J = 1.1 Hz, 1 H, H-3), 3.80 (s, 2 H, H-1'), 2.40 (d, J = 1.1 Hz, 3 H, Me-4), 2.32 (s, 3 H, H-3').

Anal. Calcd. for $C_{13}H_{12}O_3S$ (248.3): C, 62.88; H, 4.87; S, 12.91. Found: C, 62.62; H, 4.62; S, 12.70.

4,6-Dimethyl-7-(1'-methylacetonyl)mercaptocoumarin (**19**).

This compound was prepared from 4,6-dimethyl-7-mercaptocoumarin (**11**), using 3-chlorobutan-2-one, in an analogous manner to **13**. The crude reaction mixture was purified by column chromatography, yielding pure 4,6-dimethyl-7-(1'-methylacetonyl)mercaptocoumarin (**19**) (71%) from the first fraction, mp 143-144°; ^{1}H nmr (deuteriochloroform): δ 7.35 (d, J = 0.5, 1 H, H-5), 7.20 (s, 1 H, H-8), 6.23 (q, J = 1.2 Hz, 1 H, H-3), 3.95 (q, J = 7.1 Hz, 1 H, H-1'), 2.41 (d, J = 0.5 Hz, 3 H, Me-6), 2.40 (d, J = 1.2 Hz, 3 H, Me-4), 2.21 (s, 3 H, H-3'), 1.55 (d, J = 7.1 Hz, 3 H, Me-1').

Anal. Calcd. for $C_{15}H_{16}O_3S$ (276.4): C, 65.19; H, 5.83; S, 11.60. Found: C, 64.97; H, 5.65; S, 11.42.

7-Acetonylmercapto-4,6-dimethylcoumarin (**20**).

This compound was prepared from 4,6-dimethyl-7-mercaptocoumarin (**11**), using chloroacetone, in an analogous manner to **13**, mp 183-185° (methanol, 72%); ^{1}H nmr (deuteriochloroform): δ 7.33 (q, J = 0.9 Hz, 1 H, H-5), 7.03 (s, 1 H, H-8), 6.21 (q, J = 1.3 Hz, 1 H, H-3), 3.84 (s, 2 H, H-1'), 2.41 (d, J =

0.9 Hz, 3 H, Me-6), 2.40 (d, J = 1.3 Hz, 3 H, Me-4), 2.34 (s, 3 H, H-3').

Anal. Calcd. for $C_{14}H_{14}O_3S$ (262.3): C, 64.10; H 5.38; S, 12.22. Found: C, 63.91; H, 5.28; S, 12.05.

7-Acetonylmercapto-4,8-dimethylcoumarin (**21**).

This compound was prepared from 4,8-dimethyl-7-mercaptocoumarin (**12**), using chloroacetone, in an analogous manner to **13**, mp 127-128° (methanol, 70%); ^{1}H nmr (deuteriochloroform): δ 7.39 (d, J = 8.4 Hz, 1 H, H-5), 7.13 (d, J = 8.4, 1 H, H-8), 6.23 (q, J = 1.2 Hz, 1 H, H-3), 3.75 (s, 2 H, H-1'), 2.49 (s, 3 H, Me-8), 2.39 (d, J = 1.2 Hz, 3 H, Me-4), 2.31 (s, 3 H, H-3').

Anal. Calcd. for $C_{14}H_{14}O_3S$ (262.3): C, 64.10; H 5.38; S, 12.22. Found: C, 64.01; H, 5.31; S, 11.99.

4,6-Dimethyl-7-propargylmercaptocoumarin (**25**).

This compound was prepared from 4,6-dimethyl-7-mercaptocoumarin (**11**), using propargyl chloride, in an analogous manner to **13**, mp 166-167° (methanol, 80%); ^{1}H nmr (deuteriochloroform): δ 7.34 (q, J = 0.7 Hz, 1 H, H-5), 7.31 (s, 1 H, H-8), 6.23 (q, J = 1.1 Hz, 1 H, H-3), 3.71 (d, J = 2.6 Hz, 2 H, H-1'), 2.41 (d, J = 1.1 Hz, 3 H, Me-4), 2.37 (d, J = 0.7 Hz, 3 H, Me-6), 2.28 (t, J = 2.6 Hz, 1 H, H-3').

Anal. Calcd. for $C_{14}H_{12}O_2S$ (244.3): C, 68.83; H, 4.95; S, 13.12. Found: C, 68.80; H, 4.75; S, 12.90.

4,8-Dimethyl-7-propargylmercaptocoumarin (**26**).

This compound was prepared from 4,8-dimethyl-7-mercaptocoumarin (**12**), using propargyl chloride, in an analogous manner to **13**, mp 167-168° (methanol, 78%); ^{1}H nmr (deuteriochloroform): δ 7.46 (d, J = 8.5 Hz, 1 H, H-5), 7.35 (d, J = 8.5 Hz, 1 H, H-6), 6.26 (q, J = 1.2 Hz, 1 H, H-3), 3.69 (d, J = 2.6 Hz, 2 H, H-1), 2.49 (s, 3 H, Me-8) 2.43 (d, J = 1.2 Hz, 3 H, Me-4), 2.25 (t, J = 2.6 Hz, 1 H, H-3').

Anal. Calcd. for $C_{14}H_{12}O_2S$ (244.3): C, 68.83; H, 4.95; S, 13.12. Found: C, 68.61; H, 4.80; S, 13.02.

4,8,9-Trimethyl-2*H*-thieno[2,3-*h*]-1-benzopyran-2-one (**15**).

A solution of 4-methyl-7-(1'-methylacetonyl)mercaptocoumarin (**13**) (0.8 g, 3.2 mmoles) in 15 ml of concentrated sulfuric acid was kept at room temperature, monitoring the reaction by tlc. After the disappearance of the starting material (45 hours), the reaction mixture was diluted with water (200 ml) and the precipitate collected by filtration. The residue was purified by column chromatography and then crystallized from methanol, yielding 0.5 g (48%) of 4,8,9-trimethyl-2*H*-thieno[2,3-*h*]-1-benzopyran-2-one (**15**), mp 178°; ^{1}H nmr (deuteriochloroform): δ 7.61 (d, J = 8.5 Hz, 1 H, H-5), 7.43 (d, J = 8.5 Hz, 1 H, H-6), 6.30 (q, J = 1.2 Hz, 1-H, H-3), 2.69 (q, J = 0.7 Hz, 3 H, Me-8), 2.50 (d, J = 1.2 Hz, 3 H, Me-4), 2.49 (q, J = 0.7 Hz, 3 H, Me-9). Analysis (hplc) showed the presence of a small but significant quantity (0.4%) of linear compound **17** (t_R of linear compound: 18.05 minutes; t_R of angular compound: 19.62 minutes).

4,9-Dimethyl-2*H*-thieno[2,3-*h*]-1-benzopyran-2-one (**16**).

To a solution of 7-acetonylmercapto-4-methylcoumarin (**14**) (0.5 g, 2.0 mmoles) in 150 ml of toluene, methanesulfonic acid (2.7 g, 28.1 mmoles) was added and the mixture was refluxed until the starting material disappeared (24 hours, ^{1}H nmr). The solution was concentrated to dryness and the residue, dissolved in chloroform, was extracted with water. The organic phase was dried and the solvent evaporated. Repeated crystallization of the residue yielded the desired angular compound **16**, although it was still contaminated with linear isomer **18**; ^{1}H nmr (deuteriochloroform) of angular isomer: δ 7.65 (d, J = 8.5 Hz, 1 H, H-5), 7.45 (d, J = 8.5 Hz, 1 H, H-6), 7.07 (broad s, 1 H, H-8), 6.27 (q, J = 1.0 Hz, 1 H, H-3), 2.77 (broad s, 3H, Me-9 or Me-4), 2.48 (broad s, 3H, Me-9 or Me-4).

4,6,7-Trimethyl-2*H*-thieno[3,2-*g*]-1-benzopyran-2-one (**17**).

To a solution of 4-methyl-7-(1'-methylacetonyl)mercaptocoumarin (**13**) (0.8 g, 3.1 mmoles) in 180 ml of absolute ethanol, a solution of potassium hydroxide (1.8 g, 32.0 mmoles) in 40 ml of absolute ethanol was added. The reaction mixture was refluxed in the dark until the starting material disappeared (5 hours, ^{1}H nmr). After cooling, the solution was acidified with diluted hydrochloric acid, the methanol evaporated and the aqueous solution extracted with ethyl acetate. The organic phase was dried with anhydrous sodium sulfate and the solvent eliminated under reduced pressure. The residue containing linear and angular products (molar ratio 3:1) was purified by crystallization. After two successive purifications, 0.40 g of apparently pure compound **17** (52%) was isolated, mp 235°; ^{1}H nmr (deuteriochloroform): δ 7.71 (s, 1 H, H-5), 7.69 (s, 1 H, H-9), 6.30 (q, J = 1.3 Hz, 1 H, H-3), 2.54 (d, J = 1.3 Hz, 3 H, Me-4), 2.50 (q, J = 0.8 Hz, 3 H, Me-7), 2.35 (q, J = 0.8 Hz, 3 H, Me-6). In this specimen, hplc analysis showed 2% of impurity of the angular compound **15** (t_R of linear compound: 17.9 minutes; t_R of angular compound: 19.7 minutes).

4,6-Dimethyl-2*H*-thieno[3,2-*g*]-1-benzopyran-2-one (**18**).

This compound was prepared from 7-acetonylmercapto-4-methylcoumarin (**14**) in an analogous manner to **17**. The crude reaction mixture was crystallized many times from methanol, yielding apparently pure **18** (23%), mp 253°; ^{1}H nmr (deuteriochloroform): δ 7.86 (s, 1 H, H-5), 7.79 (s, 1 H, H-9), 7.11 (q, J = 1.2 Hz, 1 H, H-7), 6.32 (q, J = 1.1 Hz, 1 H, H-3), 2.56 (d, J = 1.2 Hz, 3 H, Me-4), 2.50 (d, J = 1.1 Hz, 3 H, Me-6). In this specimen, hplc analysis showed 0.6% of impurity of the angular compound **16** (t_R of linear compound: 12.11 minutes; t_R of angular compound: 13.92 minutes).

4,6,8,9-Tetramethyl-2*H*-thieno[2,3-*h*]-1-benzopyran-2-one (**22**).

A solution of 4,6-dimethyl-7-(1'-methylacetonyl)mercaptocoumarin (**19**) (3.3 g, 11.9 mmoles) in 100 ml of concentrated sulfuric acid was kept at room temperature, monitoring the reaction by ^{1}H nmr. After the disappearance of the starting material (2 hours), the reaction mixture was diluted with water, neutralized with sodium hydrogencarbonate, and extracted with ethyl acetate. The organic phase was dried and the solvent eliminated. The residue was crystallized from methanol, yielding 4,6,8,9-tetramethyl-2*H*-thieno[2,3-*h*]-1-benzopyran-2-one (**22**) (2.5 g, 85%), mp 197-198°; ^{1}H nmr (deuteriochloroform): δ 7.20 (q, J = 0.9, 1 H, H-5), 6.27 (q, J = 1.2 Hz, 1-H, H-3), 2.68 (q, J = 0.8 Hz, 3 H, Me-8), 2.52 (d, J = 0.9 Hz, 3 H, Me-6), 2.50 (q, J = 0.8 Hz, 3 H, Me-9), 2.48 (d, J = 1.2 Hz, 3 H, Me-4).

Anal. Calcd. for $C_{15}H_{14}O_2S$ (258.3): C, 69.74; H, 5.46; S, 12.41. Found: C, 69.62; H, 5.40; N, 12.37.

4,6,9-Trimethyl-2*H*-thieno[2,3-*h*]-1-benzopyran-2-one (**23**).

This compound was prepared from 7-acetonylmercapto-4,6-dimethylcoumarin (**20**) in an analogous manner to **22**, mp 194-196° (methanol, 78%); ^{1}H nmr (deuteriochloroform): δ 7.29 (q, J = 0.8 Hz, 1 H, H-5), 7.10 (q, J = 1.0 Hz, 1 H, H-8), 6.30 (q, J =

1.2 Hz, 1 H, H-3), 2.82 (d, J = 1.2 Hz, 3 H, Me-4), 2.58 (d, J = 0.8 Hz, 3 H, Me-6), 2.51 (d, J = 1.0 Hz, 3 H, Me-9).

Anal. Calcd. for $C_{14}H_{12}O_2S$ (244.3): C, 68.83; H, 4.95; S, 13.12. Found: C, 68.75; H, 4.90; S, 13.03.

4,6,9-Trimethyl-2*H*-thieno[3,2-*g*]-1-benzopyran-2-one (**24**).

This compound was prepared from 7-acetonylmercapto-4,8-dimethylcoumarin (**21**) in an analogous manner to **22**, mp 220° (methanol, 78%); ^{1}H nmr (deuteriochloroform): δ 7.66 (s, 1 H, H-5), 7.07 (q, J = 1.3 Hz, 1 H, H-7), 6.27 (q, J = 1.2 Hz, 1 H, H-3), 2.59 (s, 3 H, Me-9), 2.48 (d, J = 1.2 Hz, 3 H, Me-4), 2.46 (d, J = 1.3 Hz, 3H, Me-6).

Anal. Calcd. for $C_{14}H_{12}O_2S$ (244.3): C, 68.83; H, 4.95; S, 13.12. Found: C, 68.64; H, 4.89; S, 13.01.

4,6,8-Trimethyl-2*H*-thieno[2,3-*h*]-1-benzopyran-2-one (**27**).

A solution of 4,6-dimethyl-7-propargylmercaptocoumarin (**25**) (1.6 g, 6.5 mmoles) in *N*,*N*-diethylaniline (30 ml) was heated in a thermostatic bath at 220° in the presence of cesium fluoride (1.0 g, 6.6 mmoles) until the starting material disappeared (7 hours, ^{1}H nmr). Cesium fluoride was eliminated and the solution diluted with ethyl acetate; the organic phase was extracted many times with diluted hydrochloric acid, dried and concentrated to dryness. The residue, containing various impurities (tlc), was purified by column chromatography. The residue of the first fractions containing a single spot was crystallized from methanol, giving 0.45 g (28%) of pure 4,6,8-trimethyl-2*H*-thieno[2,3-*h*]-1-benzopyran-2-one (**27**), mp 204-206°; ^{1}H nmr (deuteriochloroform): δ 7.46 (q, J = 1.3 Hz, 1 H, H-9), 7.22 (q, J = 0.9 Hz, 1 H, H-5), 6.27 (q, J = 1.2 Hz, 1 H, H-3), 2.65 (d, J = 1.2 Hz, 3 H, Me-4), 2.55 (d, J = 0.9 Hz, 3 H, Me-6), 2.49 (d, J = 1.3 Hz, 3 H, Me-8).

Anal. Calcd. for $C_{14}H_{12}O_2S$ (244.3): C, 68.83; H, 4.95; S, 13.12. Found: C, 68.69; H, 4.77; S, 13.00.

5,7-Dimethyl-3*H*,9*H*-thiopyran[2,3-*h*]benzopyran-9-one (**28**).

A solution of 4,6-dimethyl-7-propargylmercaptocoumarin (**25**) (0.42 g, 1.7 mmoles) in *N*,*N*-diethylaniline (30 ml) was heated in a thermostatic bath at 220° until the starting material disappeared (3 hours, tlc). The cooled solution was diluted with ethyl acetate; the organic phase was extracted many times with diluted hydrochloric acid, dried and concentrated to dryness. The brown residue was purified by column chromatography. The residue of the first fractions containing a single spot was crystallized from methanol, giving 0.31 g (75%) of pure 5,7-dimethyl-3*H*,9*H*-thiopyran[2,3-*h*]benzopyran-9-one (**28**), mp 188-189°; ^{1}H nmr (deuteriochloroform): δ 7.20 (1 H, s, H-6); 7.15 (1 H, dt, J = 10.2 and 1.5, H-1), 6.20 (1H, q, J = 1.2, H-8), 6.05 (1 H, dt, J = 10.2 and J = 5.2, H-2), 3.48 (2H, dd, J = 5.2 and J = 1.5, H-3), 2.39 (3H, d, J = 1.2, Me-7), 2.35 (3H, broad s, Me-5).

Anal. Calcd. for $C_{14}H_{12}O_2S$ (244.3): C, 68.83; H, 4.95; S, 13.12. Found: C, 68.61; H, 4.71; S, 12.97.

4,10-Dimethyl-2*H*,8*H*-thiopyran[2,3-*h*]benzopyran-9-one (**29**).

This compound was prepared from 4,8-dimethyl-7-propargylmercaptocoumarin (**26**) in an analogous manner to **28**, but heating for 24 hours. The reaction mixture, containing various impurities (tlc), was purified by column chromatography, yielding **29** (27%), mp 145°; ^{1}H nmr (deuteriochloroform): δ 7.09 (s, 1 H, H-5), 6.53 (dt, J = 10.2 and J = 1.6, 1 H, H-6), 6.20 (q, J = 1.2, 1 H, H-3), 5.95 (dt, J = 10.2 and J = 5.0, 1 H, H-7), 3.54 (dd, J = 5.0 and 1.6, 2H, H-8), 2.41 (s, 3H, Me-10), 2.39 (d, J = 1.2, 3H, Me-4).

Anal. Calcd. for $C_{14}H_{12}O_2S$ (244.3): C, 68.83; H, 4.95; S, 13.12. Found: C, 68.61; H, 4.80; S, 12.90.

UV Spectra.

The uv spectra of the new methyl derivatives of 2*H*-thieno[3,2-*g*]-1-benzopyran-2-one and 2*H*-thieno[2,3-*h*]-1-benzopyran-2-one have a bathochromic effect when compared with the oxygenated isomers. Peaks at 250 and 290 nm are shifted by 20-30 nm, but the spectrophotometric properties at 365 nm (the λ generally used in therapy) are quite similar.

Analogously, the uv spectra of the methyl derivatives of 2*H*-thieno[2,3-*h*]-1-benzopyran-2-one show a shift of 10 nm to the visible region.

REFERENCES AND NOTES

[1] L. Musajo and G. Rodighiero, Photophysiology, Vol 7, A. C. Giese, ed, Academic Press, New York and London, 1972, p 115.

[2] J. A. Parrrish, R. S. Stern, M. A. Pathak and T. B. Fitzpatrick, The Science of Photomedicine, J. D. Regan and J. A. Parrish, eds, Plenum Press, New York, 1982, p 595.

[3] R. L. Edelson, *J. Photochem. Photobiol. B: Biol.*, **10**, 165 (1991).

[4] M. A. Phatak in National Cancer Institute Monograph 66: Photobiologic, Toxicologic and Pharmacologic Aspects of Psoralens, M. A. Phatak, J. C. Dunnick, eds, U.S. Government Printing Office, Washington, D. C., 1984, 41.

[5] P. Rodighiero, M. Palumbo, S. Marciani Magno, P. Manzini, O. Gia, R. Piro and A. Guiotto, *J. Heterocyclic Chem.*, **23**, 1405 (1986).

[6] P. Rodighiero, A. Chilin, G. Pastorini and A. Guiotto, *J. Heterocyclic Chem.*, **24**, 1041 (1987).

[7] P. Rodighiero, A. Guiotto, A. Chilin, F. Bordin, F. Baccichetti, F. Carlassare, D. Vedaldi, S. Caffieri, A. Pozzan and F. Dall'Acqua, *J. Med. Chem.*, **39**, 1293 (1996).

[8] V .S. Rao, P. Rodighiero, A. Chilin, A. Castellin, P. Manzini and A. Guiotto, *Liebigs Ann. Chem.*, 419 (1997).

[9] F. Baccichetti, C. Marzano, M. Simonato, C. Gatto, F. Carlassare, A. Chilin, P. Rodighiero and F. Bordin, *Méd. Biol. Environn.*, **23**, 7 (1995).

[10] K. Clarke, R. M. Scrowston and T. M. Sutton, *J. Chem. Soc., Perkin Trans. I*, 1196 (1973).

[11] A. E. Jakobs, L. E. Christiaens and M. J. Renson, *Tetrahedron*, **50**, 9315 (1994).

[12] G. R. Wellman, *J. Heterocyclic Chem.*, **17**, 911 (1980).