Synthesis of some Methylfurochromones as Potential Photochemotherapeutic Agents

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A number of new methylfurochromones with a linear psoralen like structure or an angular angelicin like structure were synthetized. The synthesis were performed starting from 7-hydroxychromones variously methylated on which the furan ring was built. Methyl groups have been introduced into positions which look most promising for enhancement of the photoreactivity of the compound towards DNA.

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Recently khellin, a natural compound present in *Ammi visnaga* L. and chemically classifiable as a furochromone, was employed for the photochemotherapy of vitiligo [2,3], an idiopatic disease characterized by the lack of pigmentation of some areas of the human skin. It has been demonstrated that khellin, unlike psoralen, is not phototoxic and, consequently, the treatment by this drug and sunlight is considered safe [4].

On the basis of the structural analogy of khellin and psoralen, some photobiological studies have been carried out on this compound. For instance, preliminary studies demonstrated that khellin photoreacts with the DNA of phage λ forming also inter strand cross-links [5].

By irradiation of a frozen aqueous solution of khellin in the presence of thymine, an adduct involving the double bond of the furan ring moiety of khellin was isolated [6].

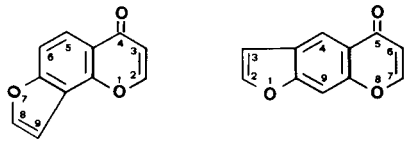
From a photobiological point of view, khellin shows a valuable phototoxicity toward various kinds of microorganisms [6] and also a valuable genotoxic activity on various biological substrates [5,6].

Owing to our interest in the field of photochemotherapeutic agents, we planned the synthesis of a series of methylfurochromones to verify if other compounds of this chemical group show the same repigmenting activity of khellin or eventually a higher photobiological activity.

The furochromones, whose synthesis we are now presenting, differ from khellin for the absence of methoxy groups; our compounds contain, on the contrary, a number of methyl groups; it is well known in fact that the presence of methyl groups in the appropriate positions enhances the photoreactivity of the molecules among the psoralen and angelicin series [7,8].

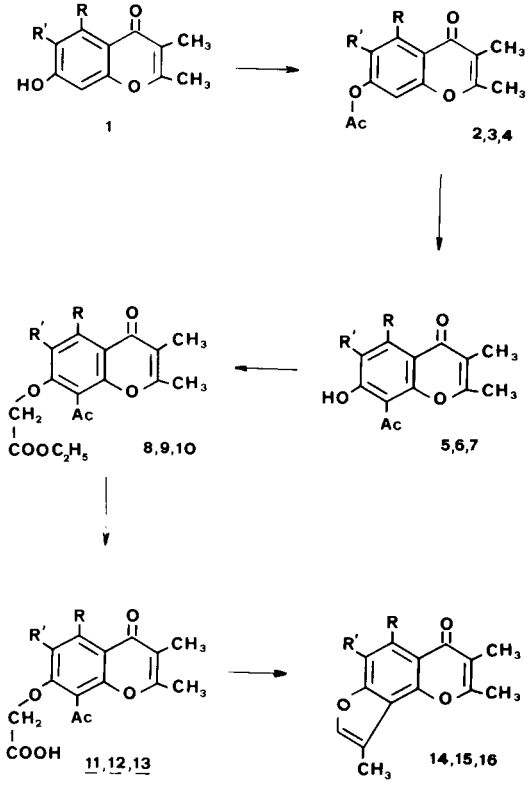
The literature is very rich in reports regarding furochromones correlated to the natural khellin, visnagin and analogous compounds, while the reports regarding methylfurochromones, free from methoxy, alkyloxy or hydroxy groups, are scarce.

We have synthetized methylfurochromones belonging to two series, presenting a linear or an angular structure, the first correlated to psoralens, linear furocoumarins, the other correlated to angelicins, angular furocoumarins.



In our synthetic method we chose to start from the appropriate methylchromones on which the furan ring was built. In this way the starting products were the appropriate 7-hydroxychromones variously methylated obtained

scheme I



3,5,8,11,14 R=R'=H

4,6,9,12,15 R=CH$_3$ R'=H

1,2,7,10,13,16 R'=CH$_3$ R=H

from the proper methylhydroxyacetophenone or methylhydroxypropiophenones by the Kostanecki-Robinson reaction. To obtain methylfurochromones carrying a methyl group in 8- position of the angular structure or in 2- position of the linear series (Scheme I and II), the 7-hydroxychromones were condensed with allyl bromide obtaining the corresponding ethers, which were submitted to the Claisen rearrangement obtaining the corresponding 6- or 8-allyl-7-hydroxychromones, according to the fact that the other *ortho* position was already occupied by a methyl group. The 6- or 8-allyl-7-hydroxychromones were then treated with bromine obtaining the 2',3'-dibromopropyl derivatives, which were cyclized in alkaline medium obtaining the desired methylfurochromones.

To obtain methylfurochromones carrying a methyl group in the 9- position of the angular structure or in 3-position of the linear series (see Scheme III and IV), the 7-acetoxychromones were submitted to the Fries rearrangement obtaining the corresponding 6- or 8-acetyl-7-hydroxychromones, according to the fact that the other *ortho* position was already occupied by a methyl group. The acetyl derivatives were then condensed with ethyl bromoacetate obtaining the corresponding ethyl esthers of 7-chromonyloxyacetic acid which were hydrolized to free acid: the lat-

scheme II

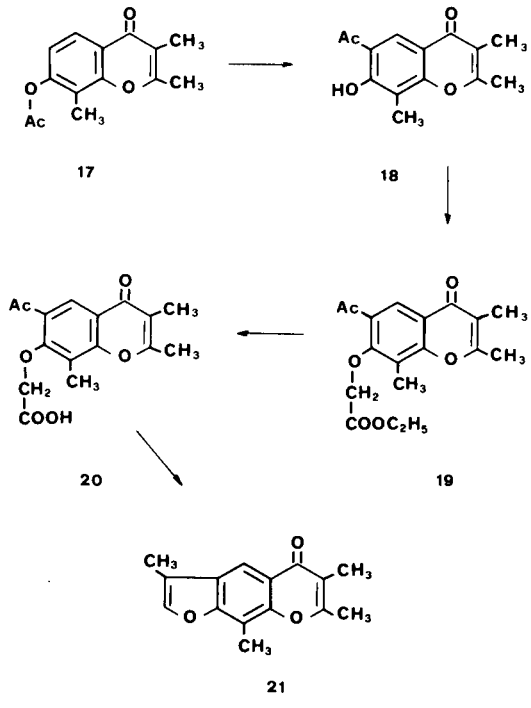
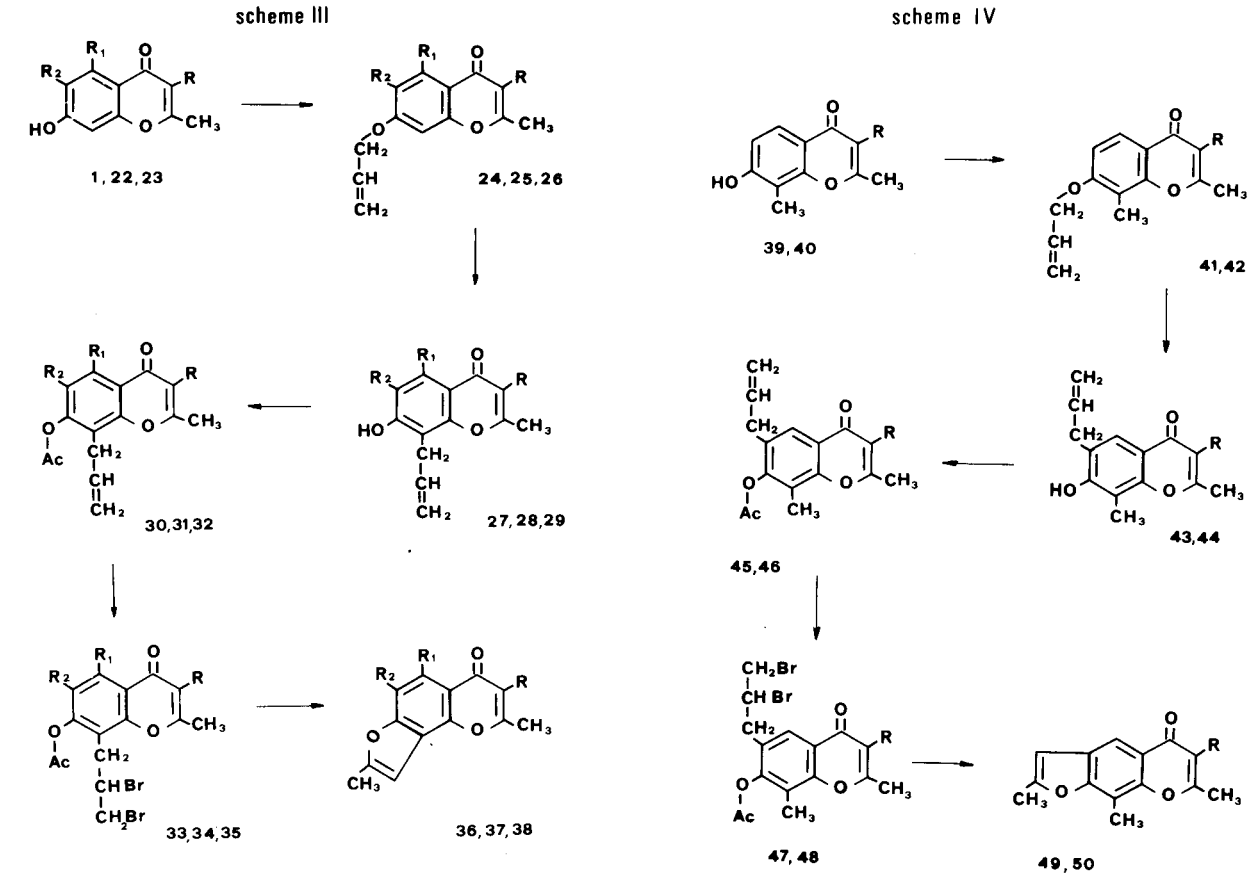


Table I

^{1}H NMR Absorptions of some Angular and Linear Methylfurochromones

Angular Type Compound	3	5	6	8	9	2Me	3Me	5Me	6Me	8Me	9Me
14	–	8.08 d J = 8.7	7.41 d J = 8.7	7.43 q J = 1.3	–	2.45 b s	2.09 b s	–	–	–	2.48 d J = 1.3
15	–	–	7.15 q J = 0.7	7.33 q J = 1.3	–	2.41 q J = 0.7	2.04 q J = 0.7	2.92 d J = 0.7	–	–	2.44 d J = 1.3
16	–	7.83 q J = 1.0	–	7.40 q J = 1.3	–	2.41 b s	2.06 b s	–	2.51 d J = 1.0	–	2.43 d J = 1.3
36	6.19 b s	8.01 d J = 8.7	7.40 d J = 8.7 d J = 0.6	–	6.68 q J = 1.0 d J = 0.6	2.42 b s	–	–	–	2.52 d J = 1.0	–
37	6.11 b s	–	7.13 b s	–	6.60 q J = 1.0 d J = 0.6	2.36 d J = 0.5	–	2.89 d J = 0.5	–	2.48 d J = 1.0	–
38	–	7.72 q J = 0.8	–	–	6.55 q J = 1.0	2.35 b s	2.35 b s	–	2.47 b s	2.47 b s	–

Linear Type Compound	2	3	4	6	2Me	3Me	6Me	7Me	9Me
21	7.46 q J = 1.3	–	8.20 b s	–	–	2.28 d J = 1.3	2.09 b s	2.45 b s	2.56 s
49	–	6.45 q J = 1.1	8.12 b s	6.15 q J = 0.7	2.49 d J = 1.1	–	–	2.42 d J = 0.7	2.58 d J = 0.5
50	–	6.42 q J = 1.0	8.09 b s	–	2.46 d J = 1.0	–	2.05 q J = 0.6	2.42 q J = 0.6	2.52 d J = 0.4



ter were cyclized in the presence of acetic anhydride and anhydrous sodium acetate to the desired methylfurochromones.

In this way the following new methylfurochromones were prepared:

2,3,9-trimethyl-4*H*-furo[2,3-*h*]-1-benzopyran-4-one, 2,3,5,9-tetramethyl-4*H*-furo[2,3-*h*]-1-benzopyran-4-one, 2,3,6,9-tetramethyl-4*H*-furo[2,3-*h*]-1-benzopyran-4-one, 3,6,7,9-tetramethyl-5*H*-furo[3,2-*g*][1]benzopyran-5-one, 2,8-dimethyl-4*H*-furo[2,3-*h*]-1-benzopyran-4-one, 2,5,8-trimethyl-4*H*-furo[2,3-*h*]-1-benzopyran-4-one, and 2,3,6,8-tetramethyl-4*H*-furo[2,3-*h*]-1-benzopyran-4-one.

In addition we have prepared by our synthetic method the 2,7,9-trimethyl-5*H*-furo[3,2-*g*][1]benzopyran-5-one and 2,6,7,9-tetramethyl-5*H*-furo[3,2-*g*][1]benzopyran-5-one, already prepared [9] by another synthetic method.

EXPERIMENTAL

Melting points (uncorrected) were determined using a Büchi-Tottoli SPM-20 capillary melting point apparatus. Analytical thin layer chromatography (tlc) was performed on pre-coated silica gel plates 60-F-254 (Merck; 0.25 mm), developing with ethyl acetate-cyclohexane mixture (35:65). Preparative column chromatography was performed using silica gel (Merck; 0.063-0.200 mm). The ^{1}H nmr spectra were recorded on a Varian FT-80A spectrometer with TMS as internal standard and deuteriochloroform as solvent unless otherwise indicated. Coupling constants are given in Hz and the relative peak areas and the decoupling experiments were in agreement with all assignments.

2,3,6-Trimethyl-7-hydroxychromone (**1**).

A solution of 2,4-dihydroxy-5-methylpropiophenone (13.7 g, 76.0 mmoles) and anhydrous sodium acetate (41.1 g, 500 mmoles) in 137 ml of acetic anhydride was heated in an oil bath at 190° for 9 hours. The reaction mixture was cautiously diluted with 100 ml of water, refluxed for 5 minutes and poured into water (300 ml). After neutralization with sodium bicarbonate the aqueous solution was extracted several times with ethyl acetate. The extracts were dried with anhydrous sodium sulphate and the solvent was evaporated. The residue containing two compounds (tlc), that is the acetylated derivative and the corresponding hydroxy derivative,

was dissolved in 400 ml of aqueous 10% solution of sodium carbonate and the solution was refluxed for 3 hours, until complete hydrolysis of the 7-acetoxy group. By acidification with diluted hydrochloric acid a solid was obtained, which was filtered, washed with water and crystallized from methanol/water (50/50; v/v) giving the 2,3,6-trimethyl-7-hydroxychromone (**1**) (5.5 g, 38%), mp 272-273°; ^{1}H nmr: δ 1.97 (broadening s, Me-3, 3H), 2.29 (broadening s, Me-6, 3H), 2.37 (broadening s, Me-2, 3H), 6.84 (s, H-8, 1H), 7.80 (broadening s, H-5, 1H).

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.42; H, 5.84.

7-Acetoxychromones **2** and **17**.

2,3,6-Trimethyl-7-acetoxychromone (**2**).

2,3,6-Trimethyl-7-hydroxychromone (**1**) (6.0 g, 29.4 mmoles) was refluxed in acetic anhydride (30 ml) containing anhydrous sodium acetate (1.0 g) for 1 hour. The reaction mixture was diluted with water (30 ml), refluxed for 10 minutes and poured into water (600 ml). The precipitate was collected, washed with water and crystallized from methanol/water (50/50, v/v) giving the 2,3,6-trimethyl-7-acetoxychromone (**2**) mp 150° (5.5 g, 76%); ^{1}H nmr: δ 2.03 (broadening s, Me-3, 3H), 2.26 (broadening s, Me-6, 3H), 2.35 (s, Ac-O-, 3H), 2.37 (broadening s, H-2, 3H), 7.11 (s, H-8, 1H), 8.03 (broadening s, H-5, 1H).

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.19; H, 5.61.

The following 7-acetoxychromone was prepared in an analogous manner:

2,3,8-Trimethyl-7-acetoxychromone (**17**).

This compound was prepared from 2,3,8-trimethyl-7-hydroxychromone mp 137° (methanol, 71%); ^{1}H nmr: δ 2.05 (broadening s, Me-3, 3H), 2.26 (s, Me-8, 3H), 2.36 (s, Ac-O-, 3H), 2.42 (broadening s, Me-2, 3H), 7.04 (d, H-6, 1H, $J_{6,5}$ = 8.7), 8.06 (d, H-5, 1H, $J_{5,6}$ = 8.7).

Fries Rearrangement (**5**, **6**, **7**, **18**).

2,3-Dimethyl-7-hydroxy-8-acetylchromone (**5**).

An accurately mixed mixture of 2,3-dimethyl-7-acetoxychromone (**3**) (3.5 g, 15.1 mmoles) and anhydrous aluminium chloride (7.0 g, 52.6 mmoles) was heated at 140° for 30 minutes. After chilling, diluted hydrochloric acid (50 ml) was added, and the mixture was refluxed for 10 minutes, diluted with water (300 ml) and extracted three times (150 ml) with ethyl acetate. The solvent was evaporated from the dried (sodium sulphate) organic phase and the pure (tlc) residue was crystallized from methanol giving 1.9 g (54%) of 2,3-dimethyl-7-hydroxy-8-acetylchromone (**5**) mp 212°; ^{1}H nmr (hexadeuterioacetone): δ 2.06 (broadening s, Me-3, 3H), 2.45 (broadening s, Me-2, 3H), 2.86 (s, Ac-8, 3H), 6.96 (d, H-6, 1H, $J_{6,5}$ = 9.0), 8.28 (d, H-5, 1H, $J_{5,6}$ = 9.0), 13.85 (s, OH-7, 1H, displayed by deuterium oxide addition).

Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.38; H, 5.19.

Analogously the following compounds were prepared:

2,3,5-Trimethyl-7-hydroxy-8-acetylchromone (**6**).

This compound was prepared from 2,3,5-trimethyl-7-acetoxychromone (**4**) mp 175° (methanol, 70%); ^{1}H nmr (hexadeuterioacetone): δ 1.97 (broadening s, Me-3, 3H), 2.48 (broadening s, Me-2, 3H), 2.78 (d, Me-5, 3H, $J_{5Me,6}$ = 0.9), 2.86 (s, Ac-8, 3H), 6.71 (q, H-6, 1H, $J_{6,5Me}$ = 0.9).

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.17; H, 5.75.

2,3,6-Trimethyl-7-hydroxy-8-acetylchromone (**7**).

This compound was prepared from 2,3,6-trimethyl-7-acetoxychromone (**2**) mp 186° (methanol, 68%); ^{1}H nmr (hexadeuterioacetone): δ 2.04 (broadening s, Me-3, 3H), 2.29 (d, Me-6, 3H, $J_{6Me,5}$ = 0.6), 2.44 (broadening s, Me-2, 3H), 2.85 (s, Ac-8, 3H), 8.13 (broadening s, H-5, 1H), 14.23 (s, OH-7, 1H, displayed by deuterium oxide addition).

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.03; H, 5.65.

2,3,8-Trimethyl-6-acetyl-7-hydroxychromone (**18**).

This compound was prepared from 2,3,8-trimethyl-7-acetoxychromone (**17**) mp 186° (methanol, 62%); ^{1}H nmr (hexadeuterioacetone): δ 2.05 (broadening s, Me-3, 3H), 2.29 (s, Me-8, 3H), 2.42 (broadening s, Me-2, 3H), 2.73 (s, Ac-6, 3H), 8.55 (broadening s, H-5, 1H), 12.82 (s, OH-7, 1H, displayed by deuterium oxide addition).

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.17; H, 5.70.

Ethyl 7-(Chromonyloxy)acetates **8**, **9**, **10**, and **19**.

Ethyl 7-(2,3-Dimethyl-8-acetylchromonyloxy)acetate (**8**).

A solution of 2,3-dimethyl-7-hydroxy-8-acetylchromone (**5**) (3.0 g, 12.9 mmoles) in 120 ml of acetone was reacted with ethyl bromoacetate (2.15 g, 15.0 mmoles) in the presence of anhydrous potassium carbonate (10.0 g) by refluxing the mixture for 5 hours. After chilling, the potassium carbonate was filtered off and washed with fresh acetone. The pooled filtrate and acetone washings were evaporated to dryness and the residue crystallized from methanol giving 2.8 g (59%) of ethyl 7-(2,3-dimethyl-8-acetylchromonyloxy)acetate (**8**), mp 132-134°; ^{1}H nmr: δ 1.28 (t, *Me*-CH_2-, 3H, J_{Me,CH_2} = 7.2), 2.02 (broadening s, Me-3, 3H), 2.35 (broadening s, Me-2, 3H), 2.65 (s, Ac-8, 3H), 4.25 (q, Me-C*H*$_2$-, 2H, $J_{CH_2,Me}$ = 7.2), 4.76 (s, Φ-O-CH_2-, 2H), 6.85 (d, H-6, 1H, $J_{6,5}$ = 9.0), 8.18 (d, H-5, 1H, $J_{5,6}$ = 9.0).

Anal. Calcd. for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70. Found: C, 63.94; H, 5.72.

The following ethers were prepared in an analogous manner:

Ethyl 7-(2,3,5-Trimethyl-8-acetylchromonyloxy)acetate (**9**).

This compound was prepared from 2,3,5-trimethyl-7-hydroxy-8-acetylchromone (**6**) mp 140° (methanol, 63%), ^{1}H nmr: δ 1.29 (t, *Me*-CH_2-, 3H, J_{Me,CH_2} = 7.1), 1.97 (broadening s, Me-3, 3H), 2.31 (broadening s, Me-2, 3H), 2.62 (s, Ac-8, 3H), 2.83 (broadening s, Me-5, 3H), 4.26 (q, Me-C*H*$_2$-, 2H, $J_{CH_2,Me}$ = 7.1), 4.75 (s, Φ-O-CH_2-, 2H), 6.56 (broadening s, H-6, 1H).

Anal. Calcd. for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 65.15; H, 6.01.

Ethyl 7-(2,3,6-Trimethyl-8-acetylchromonyloxy)acetate (**10**).

This compound was prepared from 2,3,6-trimethyl-7-hydroxy-8-acetylchromone (**7**) mp 97° (methanol, 68%); ^{1}H nmr: δ 1.40 (t, *Me*-CH_2-, 3H, J_{Me,CH_2} = 7.2), 2.04 (q, Me-3, 3H, $J_{3Me,2Me}$ = 0.7), 2.36 (q, Me-2, 3H, $J_{2Me,3Me}$ = 0.7), 2.38 (d, Me-6, 3H, $J_{6Me,5}$ = 0.8), 2.64 (s, Ac-8, 3H), 4.27 (q, Me-C*H*$_2$-, 2H, $J_{CH_2,Me}$ = 7.2), 4.51 (s, Φ-O-CH_2-, 2H), 8.05 (q, H-5, 1H, $J_{5,6Me}$ = 0.8).

Anal. Calcd. for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 64.90; H, 6.13.

Ethyl 7-(2,3,8-Trimethyl-6-acetylchromonyloxy)acetate (**19**).

This compound was prepared from 2,3,8-trimethyl-6-acetyl-7-hydroxychromone (**18**) mp 135° (methanol, 65%); ^{1}H nmr: δ 1.31 (t, *Me*-CH_2-, 3H, J_{Me,CH_2} = 7.1), 2.05 (broadening s, Me-3, 3H), 2.43 (broadening s, Me-2, 3H), 2.45 (broadening s, Me-8, 3H), 2.65 (s, Ac-6, 3H), 4.28 (q, Me-C*H*$_2$-, 2H, $J_{CH_2,Me}$ = 7.1), 4.57 (s, Φ-O-CH_2-, 2H), 8.36 (broadening s, H-5, 1H).

Anal. Calcd. for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 64.95; H, 6.05.

7-(Chromonyloxy)acetic Acids **11**, **12**, **13**, and **20**.

7-(2,3-Dimethyl-8-acetylchromonyloxy)acetic Acid (**11**).

An aqueous 5% sodium bicarbonate solution (20 ml) was added to a dioxane (100 ml) solution of ethyl 7-(2,3-dimethyl-8-acetylchromonyloxy)-acetate (**8**) (1.5 g, 4.7 mmoles) and the mixture was refluxed for 15 minutes. After chilling, the solution was acidified with diluted hydrochloric acid, water (200 ml) was added, the solid was filtered, and washed many times with water. The solid was crystallized from ethyl acetate giving 7-(2,3-dimethyl-8-acetylchromonyloxy)acetic acid (**11**) (1.1 g, 81%) mp 240°; ^{1}H nmr (hexadeuterioacetone): δ 2.04 (broadening s, Me-3, 3H), 2.39 (broadening s, Me-2, 3H), 2.62 (s, Ac-8, 3H), 5.01 (s, Φ-O-CH_2-, 2H), 7.27 (d, H-6, 1H, $J_{6,5}$ = 9.0), 8.19 (d, H-5, 1H, $J_{5,6}$ = 9.0).

Anal. Calcd. for $C_{15}H_{14}O_6$: C, 62.06; H, 4.86. Found: C, 61.92; H, 4.82.

The following 7-chromonyloxyacetic acids were prepared in an analogous manner:

7-(2,3,5-Trimethyl-8-acetylchromonyloxy)acetic Acid (**12**).

This compound was prepared from ethyl 7-(2,3,5-trimethyl-8-acetylchromonyloxy)acetate (**9**) mp 253° (ethyl acetate, 78%); ^{1}H nmr (hexadeuterioacetone): δ 1.94 (broadening s, Me-3, 3H), 2.34 (broadening s, Me-2, 3H), 2.58 (s, Ac-8, 3H), 2.81 (broadening s, Me-5, 3H), 4.97 (s, Φ-O-CH_2-, 2H), 6.96 (broadening s, H-6, 1H).

Anal. Calcd. for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 62.96; H, 5.27.

7-(2,3,6-Trimethyl-8-acetylchromonyloxy)acetic Acid (**13**).

This compound was prepared from ethyl 7-(2,3,6-trimethyl-8-acetylchromonyloxy)acetate (**10**) mp 210° (methanol, 79%); ^{1}H nmr (hexadeuterioacetone): δ 2.00 (broadening s, Me-3, 3H), 2.43 (broadening s, Me-2 and Me-6, 6H), 2.66 (s, Ac-8, 3H), 4.64 (s, Φ-O-CH_2-, 2H), 7.97 (q, H-5, 1H, $J_{5,6Me}$ = 0.8).

Anal. Calcd. for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 63.06; H, 5.20.

7-(2,3,8-Trimethyl-6-acetylchromonyloxy)acetic Acid (**20**).

This compound was prepared from ethyl 7-(2,3,8-trimethyl-6-acetylchromonyloxy)acetate (**19**) mp 210-212° (ethyl acetate, 76%); ^{1}H nmr (hexadeuterioacetone): δ 2.05 (s, Me-3, 3H), 2.41 (s, Me-2, 3H), 2.44 (s, Me-8, 3H), 2.65 (s, Ac-6, 3H), 4.59 (s, Φ-O-CH_2-, 2H), 8.34 (broadening s, H-5, 1H).

Anal. Calcd. for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 63.03; H, 5.33.

Cyclizations to **14**, **15**, **16**, and **21**.

2,3,9-Trimethyl-4*H*-furo[2,3-*h*]-1-benzopyran-4-one (**14**).

A mixture of 7-(2,3-dimethyl-8-acetylchromonyloxy)acetic acid (**11**) (1.1 g, 3.8 mmoles), acetic anhydride (30 ml) and anhydrous sodium acetate (5.0 g) was refluxed for 1 hour; to the chilled solution water (30 ml) was cautiously added, the mixture was refluxed for 10 minutes and poured into water (300 ml). The precipitate was collected, washed with water and crystallized from methanol giving 0.6 g (68%) of 2,3,9-trimethyl-4*H*-furo-[2,3-*h*]-1-benzopyran-4-one (**14**) mp 243°; ^{1}H nmr (see Table).

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.48; H, 5.26.

In a similar manner the following methylfurochromones were obtained:

2,3,5,9-Tetramethyl-4*H*-furo[2,3-*h*]-1-benzopyran-4-one (**15**).

This compound was prepared from 7-(2,3,5-trimethyl-8-acetylchromonyloxy)acetic acid (**12**) mp 210° (methanol, 78%); ^{1}H nmr (see Table).

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 74.39; H, 5.78.

2,3,6,9-Tetramethyl-4*H*-furo[2,3-*h*]-1-benzopyran-4-one (**16**).

This compound was prepared from 7-(2,3,6-trimethyl-8-acetylchromonyloxy)acetic acid (**13**) mp 181° (methanol, 68%); ^{1}H nmr (see Table).

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 74.27; H, 5.80.

3,6,7,9-Tetramethyl-5*H*-furo[3,2-*g*][1]benzopyran-5-one (**21**).

This compound was prepared from 7-(2,3,8-trimethyl-6-acetylchromonyloxy)acetic acid (**20**) mp 210-211° (methanol, 30%); ^{1}H nmr (see Table).

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 74.36; H, 5.83. Found: C, 74.17; H, 5.78.

Methyl-7-*O*-allyl Ethers **24**, **25**, **26**, **41**, and **42**.

2-Methyl-7-allyloxychromone (**24**).

A solution of 2-methyl-7-hydroxychromone (**22**) (7.5 g, 42.6 mmoles) in 250 ml of acetone was reacted with allyl bromide (7.5 g, 62.0 mmoles) in the presence of anhydrous potassium carbonate (12.0 g) by refluxing the mixture for 1 hour. After chilling the potassium carbonate was filtered off and washed with fresh acetone. The pooled filtrate and acetone washings were concentrated to dryness and the residue crystallized from methanol giving 3.5 g of 2-methyl-7-allyloxychromone (**24**) mp 90-92°; ^{1}H nmr: δ 2.36 (s, Me-2, 3H), 4.74 (dt, H-1', 2H, $J_{1',2'}$ = 5.1 and $J_{1',3'}$ = 1.4), 5.23-5.61 (m, H-3', 2H), 5.91-6.34 (m, H-2', 1H), 6.05 (broadening s, H-3, 1H), 6.96 (d, H-8, 1H, $J_{8,6}$ = 2.3), 7.02 (dd, H-6, 1H, $J_{6,5}$ = 8.7 and $J_{6,8}$ = 2.3), 7.96 (d, H-5, 1H, $J_{5,6}$ = 8.7).

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 71.98; H, 5.53.

The residue of the mother liquors was purified by column chromatography eluting with chloroform obtaining a further crop (1.5 g) of the desired compound (total 55%).

Analogously the following allyl ethers were prepared:

2,5-Dimethyl-7-allyloxychromone (**25**).

This compound was prepared from 2,5-dimethyl-7-hydroxychromone (**23**) mp 67° (ethyl acetate/cyclohexane, 65%); ^{1}H nmr: δ 2.27 (d, Me-2, 3H, $J_{2Me,3}$ = 0.7), 2.79 (d, Me-5, 3H, $J_{5Me,6}$ = 0.5), 4.58 (dt, H-1', 2H, $J_{1',2'}$ = 5.1 and $J_{1',3'}$ = 1.4), 5.24-5.53 (m, H-3', 2H), 5.83-6.30 (m, H-2', 1H), 5.99 (q, H-3, 1H, $J_{3,2Me}$ = 0.7), 6.66 (s, H-6 and H-8, 2H).

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 72.96; H, 6.04.

2,3,6-Trimethyl-7-allyloxychromone (**26**).

This compound was prepared from 2,3,6-trimethyl-7-hydroxychromone (**1**) mp 89-91° (methanol, 61%); ^{1}H nmr: δ 2.08 (broadening s, Me-3, 3H), 2.35 (broadening s, Me-2 or Me-6, 3H), 2.38 (broadening s, Me-2 or Me-6, 3H), 4.61 (broadening d, H-1', 2H, $J_{1',2'}$ = 5.0), 5.23-5.65 (m, H-3', 2H), 5.95-6.38 (m, H-2', 1H), 6.61 (s, H-6, 1H), 7.90 (broadening s, H-5, 1H).

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.59; H, 6.48.

2,8-Dimethyl-7-allyloxychromone (**41**).

This compound was prepared from 2,8-dimethyl-7-hydroxychromone (**39**) mp 99-101° (ethyl acetate, 68%); ^{1}H nmr: δ 2.32 (s, Me-2 or Me-8, 3H), 2.38 (s, Me-2 or Me-8, 3H), 4.66 (dt, H-1', 1H, $J_{1',2'}$ = 4.9 and $J_{1',3'}$ = 1.4), 5.24-5.57 (m, H-3', 2H), 5.86-6.34 (m, H-2', 1H), 6.08 (broadening s, H-3, 1H), 6.92 (d, H-6, 1H, $J_{6,5}$ = 8.8), 7.94 (d, H-5, 1H, $J_{5,6}$ = 8.8).

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 72.90; H, 6.08.

2,3,8-Trimethyl-7-allyloxychromone (**42**).

This compound was prepared from 2,3,8-trimethyl-7-hydroxychromone (**40**) mp 134° (ethyl acetate, 74%); ^{1}H nmr: δ 2.03 (q, Me-2, 3H, $J_{2Me,3Me}$ = 0.7), 2.30 (broadening s, Me-8, 3H), 2.39 (q, Me-3, 3H, $J_{3Me,2Me}$ = 0.7), 4.64 (dt, H-1', 2H, $J_{1',2'}$ = 4.9 and $J_{1',3'}$ = 1.5), 5.21-5.56 (m, H-3', 2H), 5.86-6.30 (m, H-2', 1H), 6.90 (d, H-6, 1H, $J_{6,5}$ = 8.8), 8.00 (dq, H-5, 1H, $J_{5,6}$ = 8.8 and $J_{5,8Me}$ = 0.5).

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.66; H, 6.54.

Claisen Rearrangement to **27**, **28**, **29**, **43**, and **44**.

2-Methyl-7-hydroxy-8-allylchromone (**27**).

A solution of 2-methyl-7-allyloxychromone (**24**) (8.7 g, 40.2 mmoles) in *N,N*-diethylaniline (60 ml) was refluxed for 2 hours. After this time the reaction mixture was cooled and *n*-hexane was added. The precipitate obtained was collected, washed several times with *n*-hexane and crystallized from ethyl acetate giving 6.9 g (79%) of 2-methyl-7-hydroxy-8-allylchromone (**27**), mp 190-193°; ^{1}H nmr (hexadeuterioacetone): δ 2.41 (s, Me-2, 3H), 3.63 (dt, H-1', 2H, $J_{1',2'}$ = 6.4 and $J_{1',3'}$ = 1.4), 4.91-5.23 (m, H-3', 2H), 5.74-6.25 (m, H-2', 1H), 6.07 (broadening s, H-3, 1H), 7.03 (d, H-6, 1H, $J_{6,5}$ = 8.7), 7.84 (d, H-5, 1H, $J_{5,6}$ = 8.7), 9.52 (s, OH-7, 1H, displayed by deuterium oxide addition).

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.10; H, 5.54.

The following 7-hydroxy-8-allylchromones or 7-hydroxy-6-allylchromones were prepared in analogous manner:

2,5-Dimethyl-7-hydroxy-8-allylchromone (**28**).

This compound was prepared from 2,5-dimethyl-7-allyloxychromone (**25**) mp 203-206° (ethyl acetate, 68%); ^{1}H nmr (hexadeuterioacetone): δ 2.33 (d, Me-2, 3H, $J_{2Me,3}$ = 0.7), 2.68 (d, Me-5, 3H, $J_{5Me,6}$ = 0.7), 3.54 (dt, H-1', 2H, $J_{1',2'}$ = 6.2 and $J_{1',3'}$ = 1.4), 4.90-5.20 (m, H-3', 2H), 5.69-6.14 (m, H-2', 1H), 5.94 (broadening s, H-3, 1H), 6.75 (broadening s, H-6, 1H), 9.50 (broadening s, OH-7, 1H, displayed by deuterium oxide addition).

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 72.90; H, 6.05.

2,3,6-Trimethyl-7-hydroxy-8-allylchromone (**29**).

This compound was prepared from 2,3,6-trimethyl-7-allyloxychromone (**26**) mp 190-192° (methanol, 85%); ^{1}H nmr (hexadeuterioacetone): δ 1.98 (broadening s, Me-3, 3H), 2.37 (broadening s, Me-2 or Me-6, 3H), 2.43 (broadening s, Me-2 or Me-6, 3H), 3.67 (dt, H-1', 2H, $J_{1',2'}$ = 6.2 and $J_{1',3'}$ = 1.3), 4.89-5.21 (m, H-3', 2H), 5.71-6.20 (m, H-2', 1H), 7.75 (broadening s, H-5, 1H).

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.69; H, 6.49.

2,8-Dimethyl-6-allyl-7-hydroxychromone (**43**).

This compound was obtained from 2,8-dimethyl-7-allyloxychromone (**41**) mp 190-192° (ethyl acetate, 52%); ^{1}H nmr (hexadeuterioacetone): δ 2.33 (s, Me-2 or Me-8, 3H), 2.38 (s, Me-2 or Me-8, 3H), 3.50 (dt, 1'-H, 2H, $J_{1',2'}$ = 6.3 and $J_{1',3'}$ = 1.5), 5.09-5.33 (m, H-3', 2H), 5.87-6.25 (m, H-2', 1H), 6.10 (broadening s, H-3, 1H), 7.82 (s, H-5, 1H).

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 73.07; H, 6.10.

2,3,8-Trimethyl-6-allyl-7-hydroxychromone (**44**).

This compound was prepared from 2,3,8-trimethyl-7-allyloxychromone (**42**) mp 192° (ethyl acetate, 74%); ^{1}H nmr (hexadeuterioacetone): δ 1.98 (q, Me-3, 3H, $J_{3Me,2Me}$ = 0.8), 2.35 (d, Me-8, 3H, $J_{8Me,5}$ = 0.5), 2.42 (q, Me-2, 3H, $J_{2Me,3Me}$ = 0.8), 3.52 (broadening d, H-1', 2H, $J_{1',2'}$ = 6.3), 4.98-5.23 (m, 3'-H, 2H), 5.82-6.32 (m, H-2', 1H), 7.73 (q, H-5, 1H, $J_{5,8Me}$ = 0.5), 8.33 (broadening s, OH-7, 1H, displayed by deuterium oxide addition).

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.64; H, 6.58.

7-Acetoxyallylchromones **30**, **31**, **32**, **45**, and **46**.

2-Methyl-7-acetoxy-8-allylchromone (**30**).

A solution of 2-methyl-7-hydroxy-8-allylchromone (**27**) (9.0 g, 41.6 mmoles) in 90 ml of acetic anhydride was refluxed for 1 hour in the presence of anhydrous sodium acetate (5.0 g). The reaction mixture was cautiously diluted with water, refluxed for 10 minutes and poured into water (300 ml). The precipitate was collected, washed with abundant water and crystallized from cyclohexane to give 7.1 g (80%) of 2-methyl-7-acetoxy-8-allylchromone (**30**) mp 100-102°; ^{1}H nmr: δ 2.34 (s, Ac-O-, 3H), 2.39 (s, Me-2, 3H), 3.54 (dt, H-1', 2H, $J_{1',2'}$ = 6.1 and $J_{1',3'}$ = 1.4), 4.92-5.15 (m, H-3', 2H), 5.63-6.06 (m, 2'-H, 1H), 6.16 (broadening s, H-3, 1H), 7.11 (d, H-6, 1H, $J_{6,5}$ = 8.7), 8.10 (d, H-5, 1H, $J_{5,6}$ = 8.7).

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.60; H, 5.42.

Analogously the following 7-acetoxy derivatives were prepared:

2,5-Dimethyl-7-acetoxy-8-allylchromone (**31**).

This compound was prepared from 2,5-dimethyl-7-hydroxy-8-allylchromone (**28**) mp 108-110° (methanol, 76%); ^{1}H nmr: δ 2.32 (d, Me-2, 3H, $J_{2Me,3}$ = 0.7), 2.33 (s, Ac-O-, 3H), 2.80 (d, Me-5, 3H, $J_{5Me,6}$ = 0.6), 3.47 (dt, H-1', 2H, $J_{1',2'}$ = 6.1 and $J_{1',3'}$ = 1.3), 4.90-5.14 (m, H-3', 2H), 5.62-6.03 (m, H-2', 1H), 6.06 (q, H-3, 1H, $J_{3,2Me}$ = 0.7), 6.83 (q, H-6, 1H, $J_{6,5Me}$ = 0.6).

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.48; H, 5.89.

2,3,6-Trimethyl-7-acetoxy-8-allylchromone (**32**).

This compound was prepared from 2,3,6-trimethyl-7-hydroxy-8-allylchromone (**29**) mp 126-128° (methanol, 71%); ^{1}H nmr: δ 2.04 (broadening s, Me-3, 3H), 2.22 (broadening s, Me-6, 3H), 2.36 (s, Ac-O-, 3H), 2.40 (broadening s, Me-2, 3H), 3.50 (dt, H-1', 2H, $J_{1',2'}$ = 6.2 and $J_{1',3'}$ = 1.4), 4.93-5.17 (m, H-3', 2H), 5.65-6.17 (m, H-2', 1H), 7.95 (broadening s, H-5, 1H).

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.21; H, 6.23.

2,8-Dimethyl-6-allyl-7-acetoxychromone (**45**).

This compound was prepared from 2,8-dimethyl-6-allyl-7-hydroxychromone (**43**) mp 123-125° (methanol, 68%); ^{1}H nmr: δ 2.25 (s, Me-2 or Me-8, 3H), 2.36 (s, Ac-O-, 3H), 2.38 (s, Me-2 or Me-8, 3H), 3.38 (broadening d, H-1', 2H, $J_{1',2'}$ = 6.8), 4.96-5.18 (m, H-3', 2H), 5.70-6.12 (m, H-2', 1H), 6.15 (broadening s, H-3, 1H), 7.92 (broadening s, H-5, 1H).

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.43; H, 5.86.

2,3,8-Trimethyl-6-allyl-7-acetoxychromone (**46**).

This compound was prepared from 2,3,8-trimethyl-6-allyl-7-hydroxychromone (**44**) mp 122° (methanol, 65%); ^{1}H nmr: δ 2.02 (broadening s, Me-3, 3H), 2.22 (broadening s, Me-8, 3H), 2.35 (s, Ac-O-, 3H), 2.38 (broadening s, Me-2, 3H), 3.34 (broadening d, H-1', 2H, $J_{1',2'}$ = 6.4), 4.94-5.19 (m, H-3', 2H), 5.69-6.20 (m, H-2', 1H), 7.92 (q, H-5, 1H, $J_{5,8Me}$ = 0.4).

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.13; H, 6.36.

8-(2',3'-Dibromopropyl)chromones **33**, **34**, **35**, **47**, and **48**.

2-Methyl-7-acetoxy-8-(2', 3'-dibromopropyl)chromone (**33**).

An acetic acid solution containing the stoichiometric amount of bromine was dropped at room temperature during 20 minutes into an acetic acid solution (100 ml) of 2-methyl-7-acetoxy-8-allylchromone (**30**) (7.5 g, 29.0 mmoles). After the addition was completed, the solution was further stirred for 30 minutes, the solvent was evaporated to dryness and the residue crystallized from methanol giving 2-methyl-7-acetoxy-8-(2',3'-dibromopropyl)chromone (**33**) (6.2 g, 51%) mp 153-155°; ^{1}H nmr: δ 2.40 (s, Ac-O-, 3H), 2.41 (broadening s, Me-2, 3H), 3.04-4.03 (m, H-1' and H-3', 4H), 4.23-4.54 (m, H-2', 1H), 7.18 (d, H-6, 1H, $J_{6,5}$ = 8.8), 8.14 (d, H-5, 1H, $J_{5,6}$ = 8.8).

Anal. Calcd. for $C_{15}H_{14}Br_2O_4$: C, 43.09; H, 3.37; Br, 38.23. Found: C, 42.96; H, 3.34; Br, 37.91.

The following dibromopropyl derivatives were prepared in an analogous manner:

2,5-Dimethyl-7-acetoxy-8-(2',3'-dibromopropyl)chromone (**34**).

This compound was prepared from 2,5-dimethyl-7-acetoxy-8-allylchromone (**31**) mp 162-164° (methanol, 58%); ^{1}H nmr: δ 2.36 (d, Me-2, 3H, $J_{2Me,3}$ = 0.7), 2.38 (s, Ac-O-, 3H), 2.82 (d, Me-5, 3H, $J_{5Me,6}$ = 0.7), 3.17-4.01 (m, H-1' and H-3', 4H), 4.24-4.52 (m, H-2', 1H), 6.09 (q, H-3, 1H, $J_{3,2Me}$ = 0.7), 6.91 (q, H-6, 1H, $J_{6,5Me}$ = 0.7).

Anal. Calcd. for $C_{16}H_{16}Br_2O_4$: C, 44.47; H, 3.73; Br, 36.99. Found: C, 44.28; H, 3.68; Br, 36.70.

2,3,6-Trimethyl-7-acetoxy-8-(2',3'-dibromopropyl)chromone (**35**).

This compound was prepared from 2,3,6-trimethyl-7-acetoxy-8-allylchromone (**32**) mp 169-171° (methanol, 71%); ^{1}H nmr: δ 2.04 (broadening s, Me-3, 3H), 2.24 (d, Me-6, 3H, $J_{6Me,5}$ = 0.7), 2.42 (broadening s, Me-2 and Ac-O-, 6H), 3.06-4.05 (m, H-1' and H-3', 4H), 4.24-4.56 (m, H-2', 1H), 8.02 (broadening s, H-5, 1H).

Anal. Calcd. for $C_{17}H_{18}Br_2O_4$: C, 45.76; H, 4.07; Br, 35.82. Found: C, 45.51; H, 4.00; Br, 35.59.

2,8-Dimethyl-6-(2',3'-dibromopropyl)-7-acetoxychromone (**47**).

This compound was prepared from 2,8-dimethyl-6-allyl-7-acetoxychromone (**45**) mp 140° (methanol, 65%); ^{1}H nmr: δ 2.26 (broadening s, Me-2 or Me-8, 3H), 2.39 (broadening s, Me-2 or Me-8, 3H), 2.44 (s, Ac-O-, 3H), 3.53-4.02 (m, H-1' and H-3', 4H), 4.15-4.48 (m, H-2', 1H), 6.16 (broadening s, H-3, 1H), 8.01 (broadening s, H-5, 1H).

Anal. Calcd. for $C_{16}H_{16}Br_2O_4$: C, 44.47; H, 3.73; Br, 36.99. Found: C, 44.35; H, 3.70; Br, 36.79.

2,3,8-Trimethyl-6-(2',3'-dibromopropyl)-7-acetoxychromone (**48**).

This compound was prepared from 2,3,8-trimethyl-6-allyl-7-acetoxychromone (**46**) mp 163° (methanol, 68%); ^{1}H nmr: δ 2.04 (broadening s, Me-3, 3H), 2.24 (broadening s, Me-8, 3H), 2.43 (s, Me-2 and Ac-O-, 6H), 3.56-4.07 (m, H-1' and H-3', 4H), 4.21-4.58 (m, H-2', 1H), 8.02 (broadening s, H-5, 1H).

Anal. Calcd. for $C_{17}H_{18}Br_2O_4$: C, 45.76; H, 4.07; Br, 35.82. Found: C, 45.58; H, 4.02; Br, 35.72.

Cyclization to **36**, **37**, **38**, **49**, and **50**.

2,8-Dimethyl-4*H*-furo[2,3-*h*]-1-benzopyran-4-one (**36**).

To an ethanolic solution (100 ml) of 2-methyl-7-acetoxy-8-(2',3'-dibromopropyl)chromone (**33**) (3.0 g, 7.2 mmoles) an ethanolic 4% potassium hydroxide solution was added until a molar ratio (chromone/potassium hydroxide) 1/10 was reached. The mixture was refluxed for 80 minutes, chilled, diluted with twice its volume of water and acidified with diluted hydrochloric acid. The precipitate obtained was collected by filtration and purified by column chromatography eluting by chloroform. From the first fractions containing a single spot (tlc) the solvent was evaporated and the solid obtained was crystallized from methanol giving 2,8-dimethyl-4*H*-furo[2,3-*h*]-1-benzopyran-4-one (**36**) mp 145-146° (0.68 g, 44%); ^{1}H nmr: (see Table).

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 72.75; H, 4.68.

Analogously the following methylfurochromones were prepared:

2,5,8-Trimethyl-4*H*-furo[2,3-*h*]-1-benzopyran-4-one (**37**).

This compound was prepared from 2,5-dimethyl-7-acetoxy-8-(2',3'-dibromopropyl)chromone (**34**) mp 152-154° (methanol, 43%); ^{1}H nmr: (see Table).

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.59; H, 5.32.

2,3,6,8-Tetramethyl-4*H*-furo[2,3-*h*]-1-benzopyran-4-one (**38**).

This compound was prepard from 2,3,6-trimethyl-7-acetoxy-8-(2',3'-dibromopropyl)chromone (**35**) mp 181-183° (methanol, 73%); ^{1}H nmr: (see Table).

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 74.21; H, 5.75.

2,7,9-Trimethyl-5*H*-furo[3,2-*g*][1]benzopyran-5-one (**49**).

This compound was prepared from 2,8-dimethyl-6-(2',3'-dibromopropyl)-7-acetoxychromone (**47**) mp 221° (methanol, 35%); ^{1}H nmr: (see Table).

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.51; H, 5.28.

2,6,7,9-Tetramethyl-5*H*-furo[3,2-*g*][1]benzopyran-5-one (**50**).

This compound was prepared from 2,3,8-trimethyl-6-(2',3'-dibromopropyl)-7-acetoxychromone (**48**) mp 240° (methanol, 18%); ^{1}H nmr: (see Table).

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 74.16; H, 5.78.

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