Synthesis of Methyl Derivatives of 8-Desmethylxanthyletine and 8-Desmethylseseline, Potential Antiproliferative Agents

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A number of new methyl derivatives of pyranocoumarins, related to 8-desmethylxanthyletine and to 8-desmethylseseline, were synthesized. The syntheses were performed by cyclization in boiling *N,N*-diethyl aniline of the propargyl or methylpropargyl ethers of the appropriate methyl derivatives of 7-hydroxycoumarin. Methyl groups have been introduced into positions which look most promising for enhancement of the photoreactivity of the compounds towards DNA.

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Linear furocoumarins, psoralens (see for reviews [1-3]), and angular furocoumarins, angelicins [4-7], are the two classes of photobiological agents on which, to date, the major part of the photochemical and photobiological studies have been performed.

Recently, other furocoumarins with a modified annulation geometry [8] or with a different molecular arrangement, such as pyridopsoralens [9], tetrahydrobenzo- and benzofurocoumarins [10-11], are under investigation for their potential antiproliferative activity.

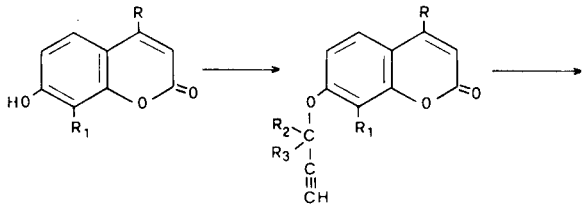
Derivatives of pyranocoumarins have also received some attentions; in particular, some desmethyl derivatives related to the two natural compounds xanthyletine and seseline have been studied from a photobiological point of view [12-14]. It has been already demonstrated that the parent xanthyletine behaves as a pure monofunctional agent, binding with DNA by means of its 3,4 double bond; however, xanthyletine photoreacts with DNA with a rate much lower than that of psoralen and this fact is probably due to the hindering effect of the two methyl groups in the 8 position to the formation of the preliminary intercalated molecular complex with the macromolecule [15].

Until now, the angular seseline has not been thoroughly tested from a photochemical point of view, but for this compound too there may be expected a monofunctional behaviour mainly due to its molecular geometry resembling that of angelicins, the well known monofunctional agents [4-7], in addition to the presence of the two hindering methyl groups in the 8-position.

In this connection and with the aim of obtaining new more active monofunctional photoreagents towards DNA, we are now reporting the synthesis of some methyl derivatives of 8-desmethylxanthyletine and of 8-desmethylseseline; methyl groups have been properly introduced in those positions which among the psoralens and angelicins series appeared to enhance the photoreactivity of the molecules [2,4,7].

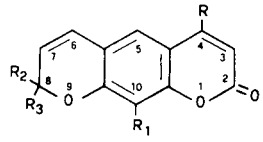
The compounds were synthesized by direct cyclization in boiling *N,N*-diethylaniline of the propargyl [16] or methylpropargyl ethers of the appropriate methylhydroxycoumarins (Scheme I, II).

Scheme I



1 R=H; R_1=I
2 R=Me; R_1=I
3 R=H; R_1=Me
4 R=R_1=Me

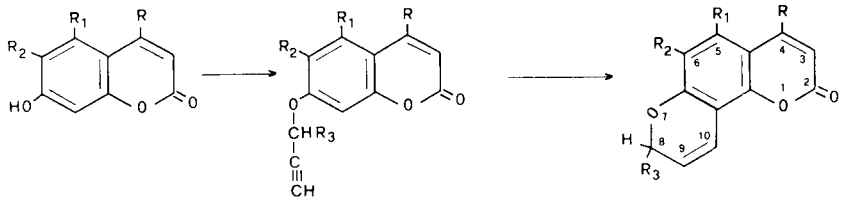
5 R=R_2=R_3=H; R_1=I
6 R=Me; R_2=R_3=H; R_1=I
7 R=R_2=R_3=H; R_1=Me
8 R=R_1=Me; R_2=R_3=H
9 R=H; R_1=R_2=R_3=Me



10 R=R_1=R_2=R_3=H
11 R=Me; R_1=R_2=R_3=H
12 R_1=Me; R=R_2=R_3=H
13 R=R_1=Me; R_2=R_3=H
14 R=H; R_1=R_2=R_3=Me

The 8 position of the coumarin nucleus is preferred in the cyclization and then, for the preparation of desmethylxanthyletine and of its methyl derivatives, this position, when not already substituted by a methyl group, was blocked by introducing into the suitable 7-hydroxycoumarins a iodine atom [17]. However, during the cyclization of propargylethers to obtain the desmethylseseline derivatives, the formation of small amounts of the isomer desmethylxanthyletine was observed and consequently the

Scheme II



15 R=Me; R_1=R_2=H
16 R_1=Me R=R_2=H
17 R_2=Me; R=R_1=H
18 R=R_2=Me; R_1=H
19 R_1=R_2=Me; R=H
20 R=R_1=R_2=H

21 R=Me; R_1=R_2=R_3=H
22 R_1=Me; R=R_2=R_3=H
23 R_2=Me; R=R_1=R_3=H
24 R=R_2=Me; R_1=R_3=H
25 R_1=R_2=Me; R=R_3=H
26 R=R_1=R_2=R_3=H
27 R=R_1=R_2=H; R_3=Me

28 R=Me; R_1=R_2=R_3=H
29 R_1=Me; R=R_2=R_3=H
30 R_2=Me; R=R_1=R_3=H
31 R=R_2=Me; R_1=R_3=H
32 R_1=R_2=Me; R=R_3=H
33 R=R_1=R_2=R_3=H
34 R=R_1=R_2=H; R_3=Me

angular pyranocoumarins were accurately purified by column chromatography.

In this way the following compounds have been prepared: 4-methyl-2*H*,8*H*-benzo[1,2-*b*;5,4-*b'*]dipyran-2-one (4-methyl-8-desmethylxanthyletine) (**11**); 4,10-dimethyl-2*H*,8*H*-benzo[1,2-*b*;5,4-*b'*]dipyran-2-one (4,10-dimethyl-8-desmethylxanthyletine) (**13**); 4-methyl-2*H*,8*H*-benzo[1,2-*b*;3,4-*b'*]dipyran-2-one (4-methyl-8-desmethylseseline) (**28**); 5-methyl-2*H*,8*H*-benzo[1,2-*b*;3,4-*b'*]dipyran-2-one (5-methyl-8-desmethylseseline) (**29**); 6-methyl-2*H*,8*H*-benzo[1,2-*b*;3,4-*b'*]dipyran-2-one (6-methyl-8-desmethylseseline) (**30**); 4,6-dimethyl-2*H*,8*H*-benzo[1,2-*b*;3,4-*b'*]-dipyran-2-one (4,6-dimethyl-8-desmethylseseline) (**31**); 5,6-dimethyl-2*H*,8*H*-benzo[1,2-*b*;3,4-*b'*]dipyran-2-one (5,6-dimethyl-8-desmethylseseline) (**32**); 8-methyl-2*H*,8*H*-benzo-[1,2-*b*;3,4-*b'*]dipyran-2-one (8-methyl-8-desmethylseseline) (**34**).

In addition and to have some compounds for comparison purpose, the 2*H*,8*H*-benzo[1,2-*b*;5,4-*b'*]dipyran-2-one (8-desmethylxanthyletine) (**10**), 10-methyl-2*H*,8*H*-benzo[1,2-*b*;5,4-*b'*]dipyran-2-one (10-methyl-8-desmethylxanthyletine) (**12**); 8,8,10-trimethyl-2*H*,8*H*-benzo[1,2-*b*;5,4-*b'*]dipyran-2-one (10-methylxanthyletine) (**14**) and 2*H*,8*H*-benzo[1,2-*b*;3,4-*b'*]dipyran-2-one (8-desmethylseseline) (**33**) have been prepared; the synthesis of compounds **10** and **33** was already reported but was obtained by a different pathway [12].

The results of photochemical and photobiological studies, which are presented in a forthcoming paper [18], unexpectedly indicated that these new compounds are able of inducing cross-links in DNA; this feature, marked in the linear compounds, is very much reduced in the angular ones.

EXPERIMENTAL

Melting points (uncorrected) were determined using a Büchi-Tottoli SPM-20 capillary melting points 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 stated. Coupling constants are given in Hz; the relative peak areas and the decoupling experiments were in agreement with all the assignments.

8-Iodo-7-hydroxycoumarins **1**, **2**.

To an ethanolic solution (200 ml) of 10.0 g (61.7 mmoles) of 7-hydroxycoumarin 7.9 g (31.0 mmoles) of iodine and a water solution (20 ml) of 3.0 g (15.6 mmoles) of periodic acid were added and the mixture was stirred at room temperature for 2 hours. After this period the mixture was poured into water (1000 ml) and the precipitate was collected, washed with abundant water and crystallized from ethanol giving 8.2 g (46%) of 7-hydroxy-8-iodocoumarin (**1**), mp 220° (reported 210-212° [17]); nmr (hexadeuterioacetone): δ 6.22 (d, H-3, 1H, $J_{3,4}$ = 9.5), 6.99 (d, H-6, 1H, $J_{6,5}$ = 8.4), 7.55 (d, H-5, 1H, $J_{5,6}$ = 8.4), 7.86 (d, H-4, 1H, $J_{4,3}$ = 9.5), 9.97 (s, OH-7, 1H, displayed by deuterium oxide addition).

4-Methyl-7-hydroxy-8-iodocoumarin (**2**).

This compound was prepared from 4-methyl-7-hydroxycoumarin mp 257° (methanol, 58%) (reported 219-220° [17]); nmr (hexadeuterioacetone): δ 2.46 (d, Me-4, 3H, $J_{Me\text{-}4,3}$ = 1.2), 6.15 (q, H-3, 1H, $J_{3,Me\text{-}4}$ = 1.2), 7.01 (d, H-6, 1H, $J_{6,5}$ = 8.7), 7.66 (d, H-5, 1H, $J_{5,6}$ = 8.7), 9.92 (broad s, OH-7, 1H, displayed by deuterium oxide addition).

7-Hydroxycoumarins Propargyl Ethers **5**, **6**, **7**, **8**, **9**, **21**, **22**, **23**, **24**, **25**, **26**, **27**.

A solution of 4.50 g (25.5 mmoles) of 8-methyl-7-hydroxycoumarin (**3**) in 200 ml of acetone was reacted with 4.6 g (38.2 mmoles) of 3-bromo-1-propyne in the presence of anhydrous potassium carbonate (10.0 g) by refluxing the mixture for 4 hours. After cooling, the potassium carbonate was filtered off and washed with fresh acetone. From the pooled filtrate and washings the solvent was evaporated at reduced pressure and the residue was crystallized from methanol giving 3.93 g (72%) of 8-methyl-7-propargyloxycoumarin (**7**), mp 151-152°; nmr: δ 2.31 (s, Me-8, 3H), 2.54 (t, H-3', 1H, $J_{3',1'}$ = 2.6), 4.80 (d, H-1', 2H, $J_{1',3'}$ = 2.6), 6.25 (d, H-3, 1H, $J_{3,4}$ = 9.5), 6.94 (d, H-6, 1H, $J_{6,5}$ = 8.5), 7.31 (d, H-5, 1H, $J_{5,6}$ = 8.5), 7.63 (d, H-4, 1H, $J_{4,3}$ = 9.5).

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 72.87; H, 4.69.

The following coumarinyl propargyl ethers have been obtained in an analogous manner.

8-Iodo-7-propargyloxycoumarin (**5**).

This compound was prepared from 7-hydroxy-8-iodocoumarin (**1**) mp 181° (methanol, 78%); nmr: δ 2.58 (t, H-3', 1H, $J_{3',1'}$ = 2.5), 4.88 (d, H-1', 2H, $J_{1',3'}$ = 2.5), 6.28 (d, H-3, 1H, $J_{3,4}$ = 9.5), 6.97 (d, H-6, 1H, $J_{6,5}$ = 8.7), 7.44 (d, H-5, 1H, $J_{5,6}$ = 8.7), 7.58 (d, H-4, 1H, $J_{4,3}$ = 9.5).

Anal. Calcd. for $C_{12}H_7IO_3$: C, 44.20; H, 2.16; I, 38.92. Found: C, 44.12; H, 2.19; I, 38.80.

4-Methyl-7-propargyloxy-8-iodocoumarin (**6**).

This compound was prepared from 4-methyl-7-hydroxy-8-iodocoumarin (**2**) mp 230° dec (methanol, 65%); nmr: δ 2.42 (d, Me-4, 3H, $J_{Me\text{-}4,3}$ = 1.3), 2.57 (t, H-3', 1H, $J_{3',1'}$ = 2.5), 4.88 (d, H-1', 2H, $J_{1',3'}$ = 2.5), 6.18 (q, H-3, 1H, $J_{3,Me\text{-}4}$ = 1.3), 6.98 (d, H-6, 1H, $J_{6,5}$ = 8.8), 7.57 (d, H-5, 1H, $J_{5,6}$ = 8.8).

Anal. Calcd. for $C_{13}H_9IO_3$: C, 45.90; H, 2.96; I, 37.32. Found: C, 45.80; H, 2.95; I, 37.18.

4,8-Dimethyl-7-propargyloxycoumarin (**8**).

This compound was prepared from 4,8-dimethyl-7-hydroxycoumarin (**4**) mp 139-140° (methanol, 70%); nmr: δ 2.29 (s, Me-8, 3H), 2.38 (d, Me-4, 3H, $J_{Me\text{-}4,3}$ = 1.2), 2.56 (t, H-3', 1H, $J_{3',1'}$ = 2.4), 4.80 (d, H-1', 2H, $J_{1',3'}$ = 2.4), 6.11 (q, H-3, 1H, $J_{3,Me\text{-}4}$ = 1.2), 6.95 (d, H-6, 1H, $J_{6,5}$ = 8.8), 7.41 (d, H-5, 1H, $J_{5,6}$ = 8.8).

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.55; H, 5.32.

8-Methyl-7-α,α-dimethylpropargyloxycoumarin (**9**).

This compound was prepared from 8-methyl-7-hydroxycoumarin (**3**) by treatment with 3-chloro-3-methylbut-1-yne, uncrystallized (68%); nmr: δ 1.70 (s, Me-1', 6H), 2.29 (s, Me-8, 3H), 2.60 (s, H-3', 1H), 6.21 (d, H-3, 1H, $J_{3,4}$ = 9.5), 7.18 (d, H-6, 1H, $J_{6,5}$ = 8.5), 7.48 (d, H-5, 1H, $J_{5,6}$ = 8.5), 7.61 (d, H-4, 1H, $J_{4,3}$ = 9.5).

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 74.45; H, 5.78.

4-Methyl-7-propargyloxycoumarin (**21**).

This compound was prepared from 4-methyl-7-hydroxycoumarin (**15**) mp 134° (methanol, 75%); nmr: δ 2.40 (d, Me-4, 3H, $J_{Me\text{-}4,3}$ = 1.2), 2.57 (t, H-3', 1H, $J_{3',1'}$ = 2.4), 4.75 (d, H-1', 2H, $J_{1',3'}$ = 2.4), 6.15 (q, H-3, 1H, $J_{3,Me\text{-}4}$ = 1.2), 6.90 (dd, H-6, 1H, $J_{6,5}$ = 9.5 and $J_{6,8}$ = 2.2), 6.93 (d, H-8, 1H, $J_{8,6}$ = 2.2), 7.52 (d, H-5, 1H, $J_{5,6}$ = 9.5).

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 72.73; H, 4.72.

5-Methyl-7-propargyloxycoumarin (**22**).

This compound was prepared from 5-methyl-7-hydroxycoumarin (**16**) mp 162° (methanol, 73%); nmr: δ 2.47 (s, Me-5, 3H), 2.58 (t, H-3', 1H, $J_{3',1'}$ = 2.4), 4.73 (d, H-1', 2H, $J_{1',3'}$ = 2.4), 6.26 (d, H-3, 1H, $J_{3,4}$ = 9.7), 6.75 (broad s, H-6 and H-8, 2H), 7.82 (d, H-4, 1H, $J_{4,3}$ = 9.7).

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 72.81; H, 4.68.

6-Methyl-7-propargyloxycoumarin (**23**).

This compound was prepared from 6-methyl-7-hydroxycoumarin (**17**) mp 152-153° (methanol, 75%); nmr: δ 2.25 (d, Me-6, 3H, $J_{Me\text{-}6,5}$ = 0.7), 2.57 (t, H-3', 1H, $J_{3',1'}$ = 2.4), 4.77 (d, H-1', 2H, $J_{1',3'}$ = 2.4), 6.25 (d, H-3, 1H, $J_{3,4}$ = 9.6), 6.92 (s, H-8, 1H), 7.22 (broad s, H-5, 1H), 7.62 (d, H-4, 1H, $J_{4,3}$ = 9.6).

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 72.70; H, 4.67.

4,6-Dimethyl-7-propargyloxycoumarin (**24**).

This compound was prepared from 4,6-dimethyl-7-hydroxycoumarin (**18**) mp 172° (methanol, 78%); nmr: δ 2.27 (broad s, Me-6, 3H), 2.38 (d, Me-4, 3H, $J_{Me\text{-}4,3}$ = 1.2), 2.56 (t, H-3', 1H, $J_{3',1'}$ = 2.4), 4.76 (d, H-1', 2H, $J_{1',3'}$ = 2.4), 6.12 (q, H-3, 1H, $J_{3,Me\text{-}4}$ = 1.2), 6.90 (s, H-8, 1H), 7.32 (q, H-5, 1H, $J_{5,Me\text{-}6}$ = 0.6).

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.52; H, 5.29.

5,6-Dimethyl-7-propargyloxycoumarin (**25**).

This compound was prepared from 5,6-dimethyl-7-hydroxycoumarin (**19**) mp 179° (methanol, 80%); nmr: δ 2.21 (s, Me-6, 3H), 2.41 (s, Me-5, 3H), 2.55 (t, H-3', 1H, $J_{3',1'}$ = 2.4), 4.76 (d, H-1', 2H, $J_{1',3'}$ = 2.4), 6.26 (d, H-3, 1H, $J_{3,4}$ = 9.9), 6.83 (broad s, H-8, 1H), 7.91 (d, H-4, 1H, $J_{4,3}$ = 9.9).

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.55; H, 5.27.

7-Propargyloxycoumarin (**26**).

This compound was prepared from 7-hydroxycoumarin (**20**) mp 120° (methanol, 78%); nmr: 2.57 (t, H-3', 1H, $J_{3',1'}$ = 2.4), 4.75 (d, H-1', 2H, $J_{1',3'}$ = 2.4), 6.26 (d, H-3, 1H, $J_{3,4}$ = 9.5), 6.90 (dd, H-6, 1H, $J_{6,5}$ = 9.3 and $J_{6,8}$ = 2.4), 6.94 (dd, H-8, 1H, $J_{8,6}$ = 2.4 and $J_{8,4}$ = 0.5), 7.40 (d, H-5, 1H, $J_{5,6}$ = 9.3), 7.64 (broad d, H-4, 1H, $J_{4,3}$ = 9.5).

Anal. Calcd. for $C_{12}H_8O_3$: C, 71.99; H, 4.03. Found: C, 71.87; H, 3.97.

7-α-Methylpropargyloxycoumarin (**27**).

This compound was prepared from 7-hydroxycoumarin (**20**) by treatment with 3-chlorobut-1-yne mp 142° (methanol, 36%); nmr: δ 1.70 (d, Me-1', 3H, $J_{Me\text{-}1',1'}$ = 6.5), 2.53 (d, H-3', 1H, $J_{3',1'}$ = 2.1), 4.92 (qd, H-1', 1H, $J_{1',Me\text{-}1'}$ = 6.5 and $J_{1',3'}$ = 2.1), 6.26 (d, H-3, 1H, $J_{3,4}$ = 9.5), 6.91 (dd, H-6, 1H, $J_{6,5}$ = 8.2 and $J_{6,8}$ = 2.3), 6.97 (d, H-8, 1H, $J_{8,6}$ = 2.3), 7.39 (d, H-5, 1H, $J_{5,6}$ = 8.2), 7.63 (d, H-4, 1H, $J_{4,3}$ = 9.5).

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 72.86; H, 4.66.

Cyclization **10**, **11**, **12**, **13**, **14**, **28**, **29**, **30**, **31**, **32**, **33**, **34**.

A solution of 2.0 g (9.3 mmoles) of 8-methyl-7-propargyloxycoumarin (**7**) in 30 ml of *N,N*-diethylaniline was refluxed for 3 hours. After cooling, the mixture was diluted with ethyl acetate and washed twice with dilute hydrochloric acid and with water. The solvent was evaporated from the organic phase dryed over anydrous sodium sulfate and the residue chromatographed on a silica gel column eluting with chloroform. From the pooled fractions containing a pure compound (tlc) the solvent was evaporated and the residue crystallized from methanol giving 0.96 g (48%) of 10-methyl-2*H*,8*H*-benzo[1,2-*b*;5,4-*b*']dipyran-2-one (**12**), mp 156°; nmr δ 2.17 (s, Me-10, 3H), 4.93 (dd, H-8, 2H, $J_{8,7}$ = 3.4 and $J_{8,6}$ = 1.9), 5.78 (dt, H-7, 1H, $J_{7,6}$ = 10.0 and $J_{7,8}$ = 3.4), 6.16 (d, H-3, 1H, $J_{3,4}$ = 9.4), 6.37 (dt, H-6, 1H, $J_{6,7}$ = 10.0 and $J_{6,8}$ = 1.9), 6.81 (broad s, H-5, 1H), 7.52 (d, H-4, 1H, $J_{4,3}$ = 9.4).

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 72.73; H, 4.65.

The following compounds have been obtained in an analogous manner.

2*H*,8*H*-Benzo[1,2-*b*;5,4-*b*']dipyran-2-one (**10**).

This compound was prepared from 7-propargyloxy-8-iodocoumarin (**5**) mp 173-174° (methanol, 28%) (reported 173° [12]); nmr: δ 4.85 (dd, H-8, 2H, $J_{8,7}$ = 3.4 and $J_{8,6}$ = 1.9), 5.72 (dt, H-7, 1H, $J_{7,6}$ = 10.0 and $J_{7,8}$ = 3.4), 6.13 (d, H-3, 1H, $J_{3,4}$ = 9.5), 6.34 (dt, H-6, 1H, $J_{6,7}$ = 10.0 and $J_{6,8}$ = 1.9), 6.59 (s, H-8, 1H), 6.91 (s, H-5, 1H), 7.48 (d, H-4, 1H, $J_{4,3}$ = 9.5).

4-Methyl-2*H*,8*H*-benzo[1,2-*b*;5,4-*b*']dipyran-2-one (**11**).

This compound was prepared from 4-methyl-7-propargyloxy-8-iodocoumarin (**6**) mp 176-177° (methanol, 30%); nmr: δ 2.36 (d, Me-4, 3H, $J_{Me\text{-}4,3}$ = 1.2), 4.92 (dd, H-8, 2H, $J_{8,7}$ = 3.4 and $J_{8,6}$ = 2.0), 5.81 (dt, H-7, 1H, $J_{7,6}$ = 10.0 and $J_{7,8}$ = 3.4), 6.09 (q, H-3, 1H, $J_{3,Me\text{-}4}$ = 1.2), 6.44 (dt, H-6, 1H, $J_{6,7}$ = 10.0 and $J_{6,8}$ = 2.0), 6.66 (s, H-8, 1H), 7.09 (s, H-5, 1H).

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found C, 72.77; H, 4.67.

4,10-Dimethyl-2*H*,8*H*-benzo[1,2-*b*;5,4-*b*']dipyran-2-one (**13**).

This compound was prepared from 4,8-dimethyl-7-propargyloxycoumarin (**8**) mp 176-179° (methanol, 45%); nmr: δ 2.23 (d, Me-10, 3H, $J_{Me\text{-}10,5}$ = 0.5), 2.35 (d, Me-4, 3H, $J_{Me\text{-}4,3}$ = 1.2), 4.94 (dd, H-8, 2H, $J_{8,7}$ = 3.5 and $J_{8,6}$ = 1.9), 5.80 (dt, H-7, 1H, $J_{7,6}$ = 10.0 and $J_{7,8}$ = 3.4), 6.10 (q, H-3, 1H, $J_{3,Me\text{-}4}$ = 1.2), 6.44 (dt, H-6, 1H, $J_{6,7}$ = 10.0 and $J_{6,8}$ = 1.9), 6.99 (broad s, H-5, 1H).

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.61; H, 5.26.

8,8,10-Trimethyl-2*H*,8*H*-benzo[1,2-*b*;5,4-*b*']dipyran-2-one (**14**).

This compound was prepared from 8-methyl-7-α,α-dimethylpropargyloxycoumarin (**9**) mp 106-107° (methanol, 48%); nmr: δ 1.46 (s, Me-8, 6H), 2.25 (s, Me-10, 3H), 5.67 (d, H-7, 1H, $J_{7,6}$ = 9.9), 6.18 (d, H-3, 1H, $J_{3,4}$ =

9.4), 6.32 (d, H-6, 1H, $J_{6,7}$ = 9.9), 6.91 (broad s, H-5, 1H), 7.56 (d, H-4, 1H, $J_{4,3}$ = 9.4).

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 74.29; H, 5.85.

4-Methyl-2*H*,8*H*-benzo[1,2-*b*;3,4-*b'*]dipyran-2-one (**28**).

This compound was prepared from 4-methyl-7-propargyloxycoumarin (**21**) mp 156° (methanol, 35%); nmr: δ 2.34 (d, Me-4, 3H, $J_{Me\text{-}4,3}$ = 1.2), 4.90 (dd, H-8, 2H, $J_{8,9}$ = 3,5 and $J_{8,10}$ = 2.0), 5.83 (dt, H-9, $J_{9,10}$ = 10.0 and $J_{9,8}$ = 3.5), 6.09 (q, H-3, 1H, $J_{3,Me\text{-}4}$ = 1.2), 6.68 (d, H-6, 1H, $J_{6,5}$ = 8.7), 6.93 (dt, H-10, 1H, $J_{10,9}$ = 10.0 and $J_{10,8}$ = 2.0), 7.29 (d, H-5, 1H, $J_{5,6}$ = 8.7).

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 72.71; H, 4.65.

5-Methyl-2*H*,8*H*-benzo[1,2,-*b*;3,4-*b'*]dipyran-2-one (**29**).

This compound was prepared from 5-methyl-7-propargyloxycoumarin (**22**) mp 151° (methanol, 31%); nmr: δ 2.42 (d, Me-5, 3H, $J_{Me\text{-}5,6}$ = 0.5), 4.89 (dd, H-8, 2H, $J_{8,9}$ = 3.5 and $J_{8,10}$ = 2.0), 5.79 (dt, H-9, 1H, $J_{9,10}$ = 10.2 and $J_{9,8}$ = 3.5), 6.22 (d, H-3, 1H, $J_{3,4}$ = 9.8), 6.55 (qd, H-6, 1H, $J_{6,Me\text{-}5}$ = 0.5 and $J_{6,10}$ = 0.6), 6.94 (dtd, H-10, 1H, $J_{10,9}$ = 10.2, $J_{10,8}$ = 2.0 and $J_{10,6}$ = 0.6), 7.79 (d, H-4, 1H, $J_{4,3}$ = 9.8).

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 72.73; H, 4.75.

6-Methyl-2*H*,8*H*-benzo[1,2-*b*;3,4-*b'*]dipyran-2-one (**30**).

This compound was prepared from 6-methyl-7-propargyloxycoumarin (**23**) mp 153-154° (methanol, 47%); nmr δ 2.09 (d, Me-6, 3H, $J_{Me\text{-}6,5}$ = 0.7), 4.90 (dd, H-8, 2H, $J_{8,9}$ = 3.5 and $J_{8,10}$ = 1.9), 5.79 (dt, H-9, 1H, $J_{9,10}$ = 10.1 and $J_{9,8}$ = 3.5), 6.12 (d, H-3, 1H, $J_{3,4}$ = 9.5), 6.78 (dt, H-10, 1H, $J_{10,9}$ = 10.1 and $J_{10,8}$ = 1.9), 6.94 (broad s, H-5, 1H), 7.48 (d, H-4, 1H, $J_{4,3}$ = 9.5).

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 72.78; H, 4.69.

4,6-Dimethyl-2*H*,8*H*-benzo[1,2-*b*;3,4-*b'*]dipyran-2-one (**31**).

This compound was prepared from 4,6-dimethyl-7-propargyloxycoumarin (**24**) mp 148° (methanol, 51%); nmr: δ 2.20 (d, Me-6, 3H, $J_{Me\text{-}6,5}$ = 0.7), 2.35 (d, Me-4, 3H, $J_{Me\text{-}4,3}$ = 1.2), 4.93 (dd, H-8, 2H, $J_{8,9}$ = 3.5 and $J_{8,10}$ = 2.0), 5.84 (dt, H-9, 1H, $J_{9,10}$ = 10.0 and $J_{9,8}$ = 3.5), 6.10 (q, H-3, 1H, $J_{3,Me\text{-}4}$ = 1.2), 6.97 (dt, H-10, 1H, $J_{10,9}$ = 10.0 and $J_{10,8}$ = 2.0), 7.17 (broad s, H-5, 1H).

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.61; H, 5.25.

5,6-Dimethyl-2*H*,8*H*-benzo[1,2-*b*;3,4-*b'*]dipyran-2-one (**32**).

This compound was prepared from 5,6-dimethyl-7-propargyloxycoumarin (**25**) mp 187° (methanol, 49%); nmr: δ 2.14 (s, Me-6, 3H), 2.36 (s, Me-5, 3H), 4.91 (dd, H-8, 2H, $J_{8,9}$ = 3.6 and $J_{8,10}$ = 1.9), 5.81 (dt, H-9, 1H, $J_{9,10}$ = 10.0 and $J_{9,8}$ = 3.6), 6.21 (d, H-3, 1H, $J_{3,4}$ = 9.8), 6.96 (dt, H-10, 1H, $J_{10,9}$ = 10.0 and $J_{10,8}$ = 1.9), 7.87 (d, 4-H, 1H, $J_{4,3}$ = 9.8).

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.58; H, 5.26.

2*H*,8*H*-Benzo[1,2-*b*;3,4-*b'*]dipyran-2-one (**33**).

This compound was prepared from 7-propargyloxycoumarin (**26**) mp 159° (methanol, 41%) (reported 163° [12]); nmr: δ 4.93 (dd, H-8, 2H, $J_{8,9}$ = 3.5 and $J_{8,10}$ = 2.0), 5.86 (dt, H-9, 1H, $J_{9,10}$ = 10.0 and $J_{9,8}$ = 3.5), 6.22 (d, H-3, 1H, $J_{3,4}$ = 9.5), 6.70 (dd, H-6, 1H, $J_{6,5}$ = 8.5 and $J_{6,10}$ = 0.7), 6.96 (dtd, H-10, 1H, $J_{10,9}$ = 10.0, $J_{10,8}$ = 2.0 and $J_{10,6}$ = 0.7), 7.20 (d, H-5, 1H, $J_{5,6}$ =8.5), 7.58 (d, H-4, 1H, $J_{4,3}$ = 9.5).

8-Methyl-2*H*,8*H*-benzo[1,2-*b*;3,4*b'*]dipyran-2-one (**34**).

This compound was prepared from 7-α-methylpropargyloxycoumarin (**27**) uncrystallized (40%); nmr: δ 1.47 (d, Me-8, 3H, $J_{Me\text{-}8,8}$ = 6.6), 5.09 (qdd, H-8, 1H, $J_{Me\text{-}8,8}$ = 6.6, $J_{8,9}$ = 3.2 and $J_{8,10}$ = 1.8), 5.75 (dd, H-9, 1H, $J_{9,10}$ = 10.0 and $J_{9,8}$ = 3.2), 6.20 (d, H-3, 1H, $J_{3,4}$ = 9.5), 6.69 (d, H-6, 1H, $J_{6,5}$ = 8.5), 6.87 (dd, H-10, 1H, $J_{10,9}$ = 10.0 and $J_{10,8}$ = 1.8), 7.18 (d, H-5, 1H, $J_{5,6}$ = 8.5), 7.57 (d, H-4, 1H, $J_{4,3}$ = 9.5).

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 72.72; H, 4.59.

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