Methyltriazolocoumarins: New Furocoumarin Isosters as Potential Photochemotherapeutic Agents

P. Rodighiero, A. Chilin, G. Pastorini and A. Guiotto*

Department of Pharmaceutical Sciences of the Padova University,
Centro di Studio sulla Chimica del Farmaco e dei Prodotti Biologicamente Attivi, - C.N.R.,
Via Marzolo 5, I-35131 Padova, Italy

P. Manzini

Institute of Pharmaceutical Chemistry of the Trieste University,
P.le Europa 1, I-34127 Trieste, Italy

Received November 20, 1989

A number of new methyltriazolocoumarins with a linear psoralen-like structure or an angular angelicin-like structure were synthetized. The syntheses were performed starting from the appropriate methylated 7-aminocoumarins which were nitrated, reduced and successively diazotized with concomitant cyclization to form the condensed triazolo ring. The new methyltriazolocoumarins show promising spectroscopic properties which are potentially predictive of their photochemical and photobiological behaviour.

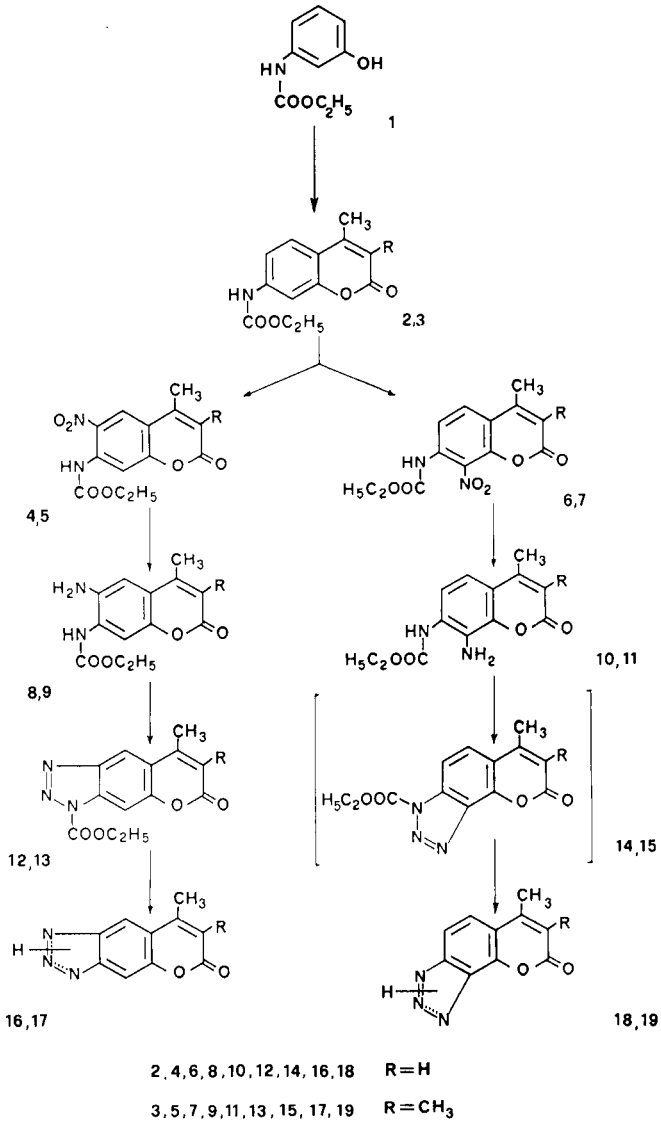
J. Heterocyclic Chem., **27**, 1153 (1990).

In the field of photochemotherapy, research is still keen in the hope of obtaining new antiproliferative agents devoid of the undesired side effects of psoralen drugs (8-methoxypsoralen, 8-MOP, and 5-methoxypsoralen, 5-MOP) currently used in PUVA therapy. These effects, such as persistent erythema, phototoxicity, possible increased risk of skin cancer [2,3] and impairment of cell-mediated immune function [4] are mostly attributed to the tendency of linear furocoumarins (psoralens) to exhibit bifunctional behaviour toward DNA, and thus form interstrand cross links [5]. Consequently, research has been aimed to obtain new compounds which show higher photoreactivity with reduced cross-linking ability. Among the essentially monofunctional reagents, angelicins [6,7], 3-carbethoxypsoralen [8,9], pyridopsoralens [10,11] and benzopsoralens [12,13] are the most promising compounds studied to date.

Recently, studies in this field dealt with the synthesis of three series of furocoumarin isosteres, namely: methylpyrrolocoumarins [14,15], methylazapsoralens [16] and methylfuroquinolinones [17]. The methylpyrrolocoumarins have been the most accurately studied in this series [18,19]. They show exclusively a monofunctional activity [19] and are completely lacking in skin phototoxicity [20]. This behaviour was mainly ascribed to the fact that the C-4′, C-5′ double bond in the pyrrole moiety is more delocalized than the corresponding furan double bond of psoralens and therefore it is prevented from behaving as a photoreactive center [19].

Considering these results, we now report a new series of methyltriazolocoumarins which may potentially act as monofunctional photoreagents toward DNA. This series consists of methylpyrano[2,3-*f*]benzotriazol-6-ones and methylpyrano[2,3-*e*]benzotriazol-8-ones, which correspond to the annulation geometry of the methylpsoralens and methylangelicins, respectively. This tricyclic triazolocou-

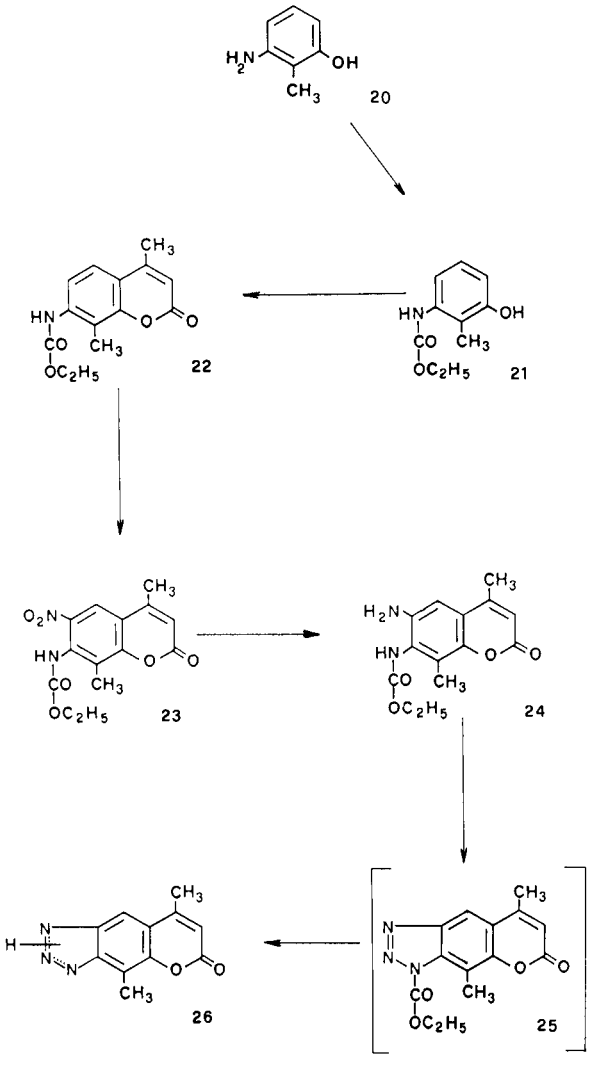
Scheme 1



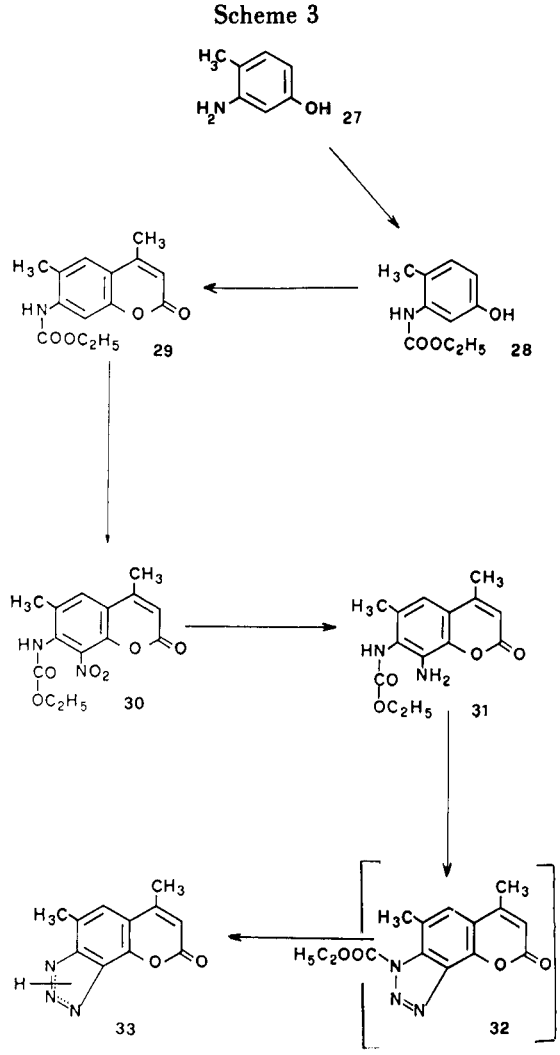
marin system has been previously reported only in one case, *i.e.*, for the unsubstituted pyrano[3,2-*e*]benzotriazol-7-one [21] which exhibited, however, a different annulation geometry. The presence of a triazolo ring, which in these isosteres replaces the furan ring of the furocoumarin nucleus, could be of some importance by possibly causing a more favourable geometry of intercalation and increasing the stability of the drug-DNA complex. The complex stability and its appropriate geometry are both essential promoting elements for the successive photoreaction events.

As illustrated by Schemes 1-3, the synthesis was started from 3-aminophenol or its 2- or 4-methyl derivatives. In each case, the corresponding urethanes were formed to prevent, in the successive reaction, the formation of 7-hydroxyquinolin-2-ones [17]. The condensation, under Pechmann conditions, of the 3-carbethoxyaminophenols with ethyl acetoacetate or its methyl derivative gave the methyl-7-carbethoxyaminocoumarins, which were nitrated with

Scheme 2



Scheme 3



nitric acid at low temperature to obtain the *ortho* nitro derivatives. When both 6- and 8- *ortho* positions were free, a mixture of 6- and 8-nitro derivatives was obtained, accompanied by trace amounts of the 6,8-dinitro derivatives, and the two useful isomers were easily isolated as pure compounds (tlc) by column chromatography. Contrary to an earlier report concerning the nitration of 4-methyl-7-carbethoxycoumarin under different conditions [22], no nitration occurred at the 3-position of the α-pyron ring under the present conditions. The nitro compounds were then reduced to the amino derivatives and then diazotized, with simultaneous cyclization of the triazolo ring.

The carbethoxy group was generally retained during the cyclization of those compounds which yielded the linear derivatives. It was, however, partially lost during the cyclization of the compounds which gave angular derivatives, as well as in the preparation of 3-carbethoxy-4,8-dimethylpyrano[2,3-*f*]benzotriazol-6-one. Owing to the potential photochemical interest of the carbethoxy derivatives, various attempts were made for obtaining

Table 1

^{1}H NMR Spectra of Pyrano[2,3-*f*]benzotriazol-6-ones

Compound	H-4	H-7	H-9	Me-4	Me-7	Me-8	$-CH_2-$	$-CH_3$
12 [a]	8.01 s	6.41 q J = 1.3	8.38 s	-	-	2.57 d J = 1.3	4.73 q J = 7.2	1.59 t J = 7.2
13 [a]	7.96 s	-	8.37 s	-	2.28 s	2.53 s	4.71 q J = 7.1	1.59 t J = 7.1
16[b]	7.70 d J = 0.7	6.39 q J = 1.3	8.38 s	-	-	2.59 d J = 1.3	-	-
17 [b]	7.67 s	-	8.35 s	-	2.23s	2.56 s	-	-
26 [b]	-	6.40 q J = 1.2	8.21 s	2.72 s	-	2.58 d J = 1.2	-	-

[a] In deuteriochloroform. [b] In deuteriomethanol. [c] Interchangeable.

Table 2

^{1}H NMR Spectra of Pyrano[2,3-e]benzotriazol-8-ones

Compound	H-4	H-5	H-7	Me-4	Me-6	Me-7
18 [b]	7.83 d(c) J = 8.9	7.74 d(c) J = 8.9	6.41 q J = 1.3	-	2.57 d J = 1.3	-
19 [b]	7.85 d(c) J = 8.9	7.73 d(c) J = 8.9	-	-	2.55 q J = 0.8	2.24 q J = 0.8
33 [b]	-	7.56 q J = 1.1	6.38 q J = 1.3	2.69 d J = 1.1	2.55 d J = 1.3	-

[a] In deuteriochloroform. [b] In deuteriomethanol. [c] Interchangeable.

their isolation. Chromatographic or fractional crystallization methods were carried out, but partial hydrolysis and decarboxylation occurred. Thus, the carbethoxy derivatives were obtained as mixtures which, according to ^{1}H nmr, also contained the decarboxylated triazolocoumarins. In all cases, hydrolysis and decarboxylation of the cyclization products furnished the linearly-or angularly-annulated title compounds.

In the triazolocoumarins prepared, methyl groups were incorporated into various positions of the molecules. From the methylpsoralen and methylangelicin series we learn that methyl groups in the appropriate positions enhance the photoreactivity of these molecules.

The spectroscopic properties of methyltriazolocoumarins are very interesting. Their uv spectra show an absorption band at *ca.* 320 nm for the linear derivatives and at *ca.* 300 nm for the angular analogs. For the linear derivatives, this band shows a red shift of *ca.* 20 nm with respect to the corresponding psoralens. In addition, this band shows a molar absorptivity much higher than that of furocoumarins. At 365 nm, the wavelength commonly used for the photochemical and photobiological experiments, the molar absorptivity of both the linear and angular compounds is much higher than that of the corresponding furocoumarins. Consequently, it is also expected that the photoreactivity of these molecules will be increased.

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 (Merck 60-F-254, 0.25 mm), which were developed with a mixture of ethyl acetate/cyclohexane (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-80 spectrometer with TMS as an 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.

Carbethoxyaminophenols **21, 28.**

2-Methyl-3-carbethoxyaminophenol (**21**).

A suspension of 1.5 g (12.2 mmoles) of 2-methyl-3-aminophenol (**20**) and 1.2 ml (12.5 mmoles) of ethyl chloroformate in 100 ml of anhydrous diethyl ether was stirred at room temperature for 2 hours. The remaining solid was filtered off and the solution was evaporated to dryness. The residue was crystallized from ethyl acetate/cyclohexane mixture to give 1.2 g (50%) of 2-methyl-3-carbethoxyaminophenol (**21**), mp 79°; ^{1}H nmr (hexadeuterioacetone): δ 7.27 (dd, H-4, 1H, J = 8.7 and J = 1.0 Hz), 7.00 (dd, H-5, 1H, J = 8.7 and J = 8.7 Hz), 6.53 (dd, H-6, 1H, J = 8.7 and J = 1.0 Hz), 6.37 (broad s, OH or NH, 1H), 4.22 (q, $-CH_2-CH_3$, 2H, J = 7.1 Hz), 2.11 (s, Me-2, 3H), 1.31 (t, $-CH_2-CH_3$, 3H, J = 7.1 Hz).

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.48; H, 6.60; N, 7.20.

4-Methyl-3-carbethoxyaminophenol (**28**).

This compound was prepared following the procedure for **21** above from 3-amino-4-methylphenol (**27**); yield of **28** was 46%, mp 118° (cyclohexane); ^{1}H nmr: δ 7.62 (broad s, -OH, 1H), 6.99 (d, H-5, 1H, J = 8.2 Hz), 6.62 (broad s, NH, 1H), 6.53 (dd, H-6, 1H, J = 8.2 and J = 2.6 Hz), 6.49 (broad s, H-2, 1H), 4.24 (q, -C*H*$_2$-CH$_3$, 2H, J = 7.1 Hz), 2.17 (s, Me-4, 3H), 1.33 (t, -CH$_2$-C*H*$_3$, 3H, J = 7.1 Hz).

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.37; H, 6.72; N, 7.15.

Methyl-7-carbethoxyaminocoumarins **2**, **3**, **22**, **29**.

3,4-Dimethyl-7-carbethoxyaminocoumarin (**3**).

A mixture of 16.8 g (92.6 mmoles) of 3-carbethoxyaminophenol (**1**), 15.7 ml (111 mmoles) of ethyl 2-methylacetoacetate and 230 ml of 70% sulfuric acid was stirred at room temperature for 4 hours. The solution was poured into 1 liter of an ice-water mixture resulting in the formation of a precipitate which was collected and crystallized from ethanol to give 15.2 g (63%) of 3,4-dimethyl-7-carbethoxyaminocoumarin (**3**), mp 199°; ^{1}H nmr: δ 7.45 (d, H-5, 1H, J = 8.8 Hz), 7.43 (d, H-8, 1H, J = 1.3 Hz), 7.37 (dd, H-6, 1H, J = 8.8 and J = 1.3 Hz), 4.25 (q, -C*H*$_2$-CH$_3$, 2H, J = 7.1 Hz), 2.36 (s, Me-4, 3H), 2.18 (s, Me-3, 3H), 1.32 (t, -CH$_2$-C*H*$_3$, 3H, J = 7.1 Hz).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.11; H, 5.67; N, 5.34.

In the same manner the following methyl-7-carbethoxycoumarins were synthesized:

4-Methyl-7-carbethoxyaminocoumarin (**2**).

This compound was prepared from 3-carbethoxyaminophenol (**1**) in 90% yield; mp 187° (ethanol) (reported [23] 186-188°); ^{1}H nmr (hexadeuteriodimethyl sulfoxide): δ 10.19 (broad s, NH, 1H), 7.76 (d, H-5, 1H, J = 8.8 Hz), 7.64 (d, H-8, 1H, J = 2.0 Hz), 7.49 (dd, H-6, 1H, J = 8.8 and J = 2.0 Hz), 6.31 (q, H-3, 1H, J = 1.2 Hz), 4.28 (q, -C*H*$_2$-CH$_3$, 2H, J = 7.1 Hz), 2.49 (d, Me-4, 3H, J = 1.2 Hz), 1.38 (t, -CH$_2$-C*H*$_3$, 3H, J = 7.1 Hz).

4,8-Dimethyl-7-carbethoxyaminocoumarin (**22**).

This compound was prepared from 2-methyl-3-carbethoxyaminophenyl (**21**) in 63% yield, mp 170° (ethanol); ^{1}H nmr: δ 7.95 (d, H-5, 1H, J = 8.8 Hz), 7.44 (d, H-6, 1H, J = 8.8 Hz), 6.19 (q, H-3, 1H, J = 1.2 Hz), 4.26 (q, -C*H*$_2$-CH$_3$, 2H, J = 7.1 Hz), 2.41 (d, Me-4, 3H, J = 1.2 Hz), 2.34 (s, Me-8, 3H), 1.34 (t, -CH$_2$-C*H*$_3$, 3H, J = 7.1 Hz).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.31; H, 5.71; N, 5.30.

4,6-Dimethyl-7-carbethoxyaminocoumarin (**29**).

This compound was prepared from the 4-methyl-3-carbethoxyaminophenol (**28**) in 75% yield mp 212° (ethanol); ^{1}H nmr: δ 7.99 (broad s, NH, 1H), 7.29 (s, H-5, 1H), 6.69 (broad s, H-8, 1H), 6.14 (broad, s, H-3, 1H), 4.27 (q, -C*H*$_2$-CH$_3$, 2H, J = 7.1 Hz), 2.38 (s, Me-4 or Me-6, 3H), 2.32 (s, Me-4 or Me-6, 3H), 1.34 (t, -CH$_2$-C*H*$_3$, 3H, J = 7.1 Hz).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.21; H, 5.77; N, 5.29.

Methyl-7-carbethoxyaminocoumarins Nitro Derivatives **4**, **5**, **6**, **7**, **23** and **30**.

4-Methyl-6-nitro-7-carbethoxyaminocoumarin (**4**) and 4-Methyl-7-carbethoxyamino-8-nitrocoumarin (**6**).

A mixture of 7.5 ml (164 mmoles) of concentrated nitric acid and 7.5 ml of concentrated sulfuric acid was slowly dropped into a solution of 12.0 g (48.5 mmoles) of 4-methyl-7-carbethoxyaminocoumarin (**2**) in 50 ml of concentrated sulfuric acid, keeping the temperature below -5°. After the addition was completed, the reaction mixture was poured into 1 liter of an ice-water mixture and the resulting precipitate was collected and washed several times with water. The solid, which essentially contained two main products (tlc), was chromatographed on a silica gel column and eluted with chloroform. The initial fractions which contained a single compound (tlc) were pooled and evaporated and the residue was crystallized from ethyl acetate, to give 7.05 g (50%) of 4-methyl-6-nitro-7-carbethoxyaminocoumarin (**4**), mp 162° (reported [22] 163-164°); ^{1}H nmr: δ 10.05 (broad s, NH, 1H), 8.58 (s, H-5 or H-8, 1H), 8.50 (s, H-5 or H-8, 1H), 6.29 (q, H-3, 1H, J = 1.3 Hz), 4.32 (q, -C*H*$_2$-CH$_3$, 2H, J = 7.1 Hz), 2.46 (d, Me-4, 3H, J = 1.3 Hz), 1.36 (t, -CH$_2$-C*H*$_3$, 3H, J = 7.1 Hz).

Subsequent fractions which contained a single product (tlc) were also pooled and evaporated and the residue was crystallized from ethyl acetate to give 3.8 g (27%) of 4-methyl-7-carbethoxyamino-8-nitrocoumarin (**6**), mp 211°; ^{1}H nmr: δ 8.26 (d, H-5, 1H, J = 9.1 Hz), 8.05 (broad s, NH, 1H), 7.69 (d, H-6, 1H, J = 9.1 Hz), 6.27 (q, H-3, 1H, J = 1.2 Hz), 4.27 (q, -C*H*$_2$-CH$_3$, 2H, J = 7.1 Hz), 2.44 (d, Me-4, 3H, J = 1.2), 1.34 (t, -CH$_2$-C*H*$_3$, 3H, J = 7.1 Hz).

Anal. Calcd. for $C_{13}H_{12}N_2O_6$: C, 53.43; H, 4.14; N, 9.59. Found: C, 53.35; H, 4.12; N, 9.51.

Under the same condition the following nitro derivatives were obtained:

3,4-Dimethyl-6-nitro-7-carbethoxyaminocoumarin (**5**) and 3,4-dimethyl-7-carbethoxyamino-8-nitrocoumarin (**7**).

These two isomers were obtained starting with 3,4-dimethyl-7-carbethoxyaminocoumarin (**3**). 3,4-Dimethyl-6-nitro-7-carbethoxyaminocoumarin (**5**) was obtained in 42% yield, mp 174° (ethyl acetate); ^{1}H nmr: δ 10.01 (broad s, NH, 1H), 8.54 (s, H-5 or H-8, 1H), 8.50 (s, H-5 or H-8, 1H), 4.30 (q, -C*H*$_2$-CH$_3$, 2H, J = 7.1 Hz), 2.42 (s, Me-4, 3H), 2.22 (s, Me-3, 3H), 1.36 (t, -CH$_2$-C*H*$_3$, 3H, J = 7.1 Hz).

Anal. Calcd. for $C_{14}H_{14}N_2O_6$: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.69; H, 4.59; N, 9.09.

3,4-Dimethyl-7-carbethoxyamino-8-nitrocoumarin (**7**) was obtained in 30% yield mp 184° (ethyl acetate); ^{1}H nmr: δ 8.22 (d, H-5, 1H, J = 9.2 Hz), 8.06 (broad s, NH, 1H), 7.70 (d, H-6, 1H, J = 9.2 Hz), 4.27 (q, C*H*$_2$-CH$_3$, 2H, J = 7.1 Hz), 2.40 (s, Me-4, 3H), 2.22 (s, Me-3, 3H), 1.34 (t, -CH$_2$-C*H*$_3$, 3H, J = 7.1 Hz).

Anal. Calcd. for $C_{14}H_{14}N_2O_6$: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.73; H, 4.55; N, 9.10.

4,8-Dimethyl-6-nitro-7-carbethoxyaminocoumarin (**23**).

This compound was prepared from 4,8-dimethyl-7-carbethoxyaminocoumarin (**22**) in 85% yield, mp 212° (methanol); ^{1}H nmr: δ 8.18 (s, H-5, 1H), 7.99 (broad s, NH, 1H), 6.37 (q, H-3, 1H, J = 1.3 Hz), 4.23 (q, -C*H*$_2$-CH$_3$, 2H, J = 7.1 Hz), 2.47 (d, Me-4, 3H, J = 1.3 Hz), 2.41 (s, Me-8, 3H), 1.32 (t, -CH$_2$-C*H*$_3$, 3H, J = 7.1 Hz).

Anal. Calcd. for $C_{14}H_{14}N_2O_6$: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.85; H, 4.60; N, 9.09.

4,6-Dimethyl-7-carbethoxyamino-8-nitrocoumarin (**30**).

This compound was prepared from 4,6-dimethyl-7-carbethoxyaminocoumarin (**29**) in 83% yield, mp 237° (methanol); ^{1}H nmr: δ 7.59 (s, H-5, 1H), 6.33 (q, H-3, 1H, J = 1.2 Hz), 4.21 (q, -C*H*$_2$-CH$_3$, 2H, J = 7.1 Hz), 2.45 (d, Me-4, 3H, J = 1.2 Hz), 2.41 (s, Me-6, 3H), 1.30 (t, -CH$_2$C*H*$_3$, 3H, J = 7.1 Hz).

Anal. Calcd. for $C_{14}H_{14}N_2O_6$: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.76; H, 4.62; N, 9.11.

Amino-7-carbethoxyaminocoumarins **8**, **9**, **10**, **11**, **24** and **31**.

4-Methyl-6-amino-7-carbethoxyaminocoumarin (**8**).

A suspension of 0.12 g of 10% palladium on carbon in 100 ml of absolute ethanol was stirred for 10 minutes in the presence of hydrogen at room pressure. A solution of 2.0 g (6.8 mmoles) of 4-methyl-6-nitro-7-carbethoxyaminocoumarin (**4**) in 1.2 liter of absolute ethanol was added and the suspension was stirred until the starting compound was completely reduced (tlc). The catalyst was removed by filtration and the solvent evaporated. The residue was crystallized from methanol giving 1.3 g (72%) of 4-methyl-6-amino-7-carbethoxyaminocoumarin (**8**), mp 198° (reported [22] 193-194°); ^{1}H nmr: δ 7.66 (s, H-5, 1H), 6.95 (s, H-8, 1H), 6.15 (q, H-3, 1H, J = 1.1 Hz), 4.25 (q, -C*H*$_2$-CH$_3$, 2H, J = 7.1 Hz), 3.54 (broad s, -NH$_2$, 2H), 2.34 (d, Me-4, 3H, J = 1.1 Hz), 1.33 (t, -CH$_2$-C*H*$_3$, 3H, J = 7.1 Hz).

In a similar manner the following amino derivatives were prepared:

3,4-Dimethyl-6-amino-7-carbethoxyaminocoumarin (**9**).

This compound was prepared from 3,4-dimethyl-6-nitro-7-carbethoxyaminocoumarin (**5**) in 79% yield, mp 207° (methanol); ^{1}H nmr: δ 7.60 (s, H-5, 1H), 6.96 (s, H-8, 1H), 4.25 (q, -C*H*$_2$-CH$_3$, 2H, J = 7.1 Hz), 2.31 (s, Me-4, 3H), 2.17 (s, Me-3, 3H), 1.33 (t, -CH$_2$-C*H*$_3$, 3H, J = 7.1 Hz).

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.72; H, 5.79; N, 10.12.

4-Methyl-7-carbethoxyamino-8-aminocoumarin (**10**).

This compound was prepared from 4-methyl-7-carbethoxyamino-8-nitrocoumarin (**6**) in 78% yield, mp 174° (methanol); ^{1}H nmr: δ 7.45 (d, H-5, 1H, J = 8.6 Hz), 7.02 (d, H-6, 1H, J = 8.6 Hz), 6.78 (broad s, NH, 1H), 6.19 (q, H-3, 1H, J = 1.2 Hz), 4.24 (q, -C*H*$_2$-CH$_3$, 2H, J = 7.1 Hz), 4.10 (broad s, -NH$_2$, 2H), 2.39 (d, Me-4, 3H, J = 1.2 Hz), 1.32 (t, -CH$_2$-C*H*$_3$, 3H, J = 7.1 Hz).

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.41; H, 5.28; N, 10.51.

3,4-Dimethyl-7-carbethoxyamino-8-aminocoumarin (**11**).

This compound was prepared from 3,4-dimethyl-7-carbethoxyamino-8-nitrocoumarin (**7**) in 77% yield, mp 199° (methanol); ^{1}H nmr: δ 7.39 (d, H-5, 1H, J = 8.7 Hz), 7.03 (d, H-6, 1H, J = 8.7 Hz), 4.24 (q, -C*H*$_2$-CH$_3$, 2H, J = 7.2 Hz), 2.36 (s, Me-4, 3H), 2.20 (s, Me-3, 3H), 1.32 (t, -CH$_2$-C*H*$_3$, 3H, J = 7.2 Hz).

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.58; H, 5.78; N, 10.01.

4,8-Dimethyl-6-amino-7-carbethoxyaminocoumarin (**24**).

This compound was prepared from 4,8-dimethyl-6-nitro-7-carbethoxyaminocoumarin (**23**) in 62% yield, mp 300° (methanol); ^{1}H nmr: δ 6.80 (s, H-5, 1H), 6.23 (q, H-3, 1H, J = 1.3 Hz), 4.23 (q, -C*H*$_2$-CH$_3$, 2H, J = 7.1 Hz), 2.35 (d, Me-4, 3H, J = 1.3), 2.34 (s, Me-8, 3H), 1.31 (t, -CH$_2$-C*H*$_3$, 3H, J = 7.1 Hz).

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.76; H, 5.81; N, 10.16.

4,6-Dimethyl-7-carbethoxyamino-8-aminocoumarin (**31**).

This compound was prepared from 4,6-dimethyl-7-carbethoxyamino-8-nitrocomarin (**30**) in 74% yield, mp 216° (methanol); ^{1}H nmr: δ 6.83 (broad s, H-5, 1H), 6.24 (q, H-3, 1H, J = 1.2 Hz), 4.24 (q, C*H*$_2$-CH$_3$, 2H, J = 7.1 Hz), 2.39 (d, Me-4, 3H, J = 1.2 Hz), 2.29 (s, Me-6, 3H), 1.32 (t, -CH$_2$-C*H*$_3$, 3H, J = 7.1 Hz).

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.62; H, 5.77; N, 10.05.

3-Carbethoxypyrano[2,3-*f*]benzotriazol-6-ones **12** and **13**.

3-Carbethoxy-8-methylpyrano[2,3-*f*]benzotriazol-6-one (**12**).

A solution of 0.10 g (1.45 mmoles) of sodium nitrite in 1.5 ml of water was dropped into a solution of 0.26 g (1.0 mmoles) of 4-methyl-6-amino-7-carbethoxyaminocoumarin (**8**) in 15 ml of concentrated hydrochloric acid with cooling under -5°. After the reaction was completed (15 minutes, tlc) the mixture was diluted with 50 ml of water and the precipitate was collected and crystallized from methanol giving 0.22 g (82%) of 3-carbethoxy-8-methylpyrano[2,3-*f*]benzotriazol-6-one (**12**), mp 191°; ^{1}H nmr: (see Table 1).

Anal. Calcd. for $C_{13}H_{11}N_3O_4$: C, 57.14; H, 4.06; N, 15.38. Found: C, 56.89; H, 3.97; N, 15.37.

In a same manner the following triazolocoumarin derivative was prepared:

3-carbethoxy-7,8-dimethylpyrano[2,3-*f*]benzotriazol-6-one (**13**).

This compound was prepared from 3,4-dimethyl-6-amino-7-carbethoxyaminocoumarin (**9**) in 75% yield, mp 193° (methanol); ^{1}H nmr: (see Table 1).

Anal. Calcd. for $C_{14}H_{13}N_3O_4$: C, 58.53; H, 4.56; N, 14.63. Found: C, 58.41; H, 4.49; N, 14.61.

Pyrano[2,3-*f*]benzotriazol-6-ones **16**, **17** and **26**.

8-Methylpyrano[2,3-*f*]benzotriazol-6-one (**16**).

A solution of 0.30 g (1.1 mmoles) of 3-carbethoxy-8-methylpyrano[2,3-*f*]benzotriazol-6-one (**12**) in concentrated sulfuric acid (6.5 ml) and acetic acid (12.5 ml) was refluxed for 30 minutes. The solution was then poured into 300 ml of an ice-water mixture. The precipitate was collected, washed several times with water and crystallized from ethanol giving 0.14 g (64%) of 8-methylpyran[2,3-*f*]benzotriazol-6-one (**16**), mp 250° dec; ^{1}H nmr: see Table 1.

Anal. Calcd. for $C_{10}H_7N_3O_2$: C, 59.70; H, 3.51; N, 20.89. Found: C, 59.48; H, 3.46; N, 20.79.

Under the same conditions the following decarboxylate derivatives were obtained:

7,8-Dimethylpyrano[2,3-*f*]benzotriazol-6-one (**17**).

This compound was prepared from 3-carbethoxy-7,8-dimethylpyrano[2,3-*f*]benzotriazol-6-one (**13**) in 65% yield, mp 288° (methanol); ^{1}H nmr: see Table 1.

Anal. Calcd. for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.22; H, 4.23; N, 19.35.

4,8-Dimethylpyrano[2,3-*f*]benzotriazol-6-one (**26**).

This compound was prepared by condensing the triazolo ring on 4,8-dimethyl-6-amino-7-carbethoxyaminocoumarin (**24**) by treatment with sodium nitrite in acidic medium as described for compound **16**. The crude product was a mixture of 3-carbethoxy-4,8-dimethylpyrano[2,3-*f*]benzotriazol-6-one (**25**) and 4,8-dimethylpyrano[2,3-*f*]benzotriazol-6-one (**26**). Attempts to isolate

the 3-carbethoxy derivative **25** gave a product containing trace amount of decarboxylate compound **26**. The crude product was then subjected to the hydrolysis and decarboxylation steps as described in the above-reported procedure to obtain 4,8-dimethylpyrano[2,3-*f*]benzotriazol-6-one (**26**) in 65% yield, mp 300° (methanol); ^{1}H nmr: see Table 1.

Anal. Calcd. for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.22; H, 4.15; N, 19.48.

In the same manner the following angular triazolocoumarins were obtained:

Methylpyrano[2,3-*e*]benzotriazol-8-one **18**, **19** and **33**.

6-Methylpyrano[2,3-*e*]benzotriazol-8-one (**18**).

This compound was prepared from 4-methyl-7-carbethoxyamino-8-aminocoumarin (**10**) in 60% yield, mp 300° dec (methanol); ^{1}H nmr: see Table 2.

Anal. Calcd. for $C_{10}H_7N_3O_2$: C, 59.70; H, 3.51; N, 20.89. Found: C, 59.52; H, 3.48; N, 20.85.

6,7-Dimethylpyrano[2,3-*e*]benzotriazol-8-one (**19**).

This compound was prepared from 3,4-dimethyl-7-carbethoxyamino-8-aminocoumarin (**11**) in 60% yield, mp 300° (methanol); ^{1}H nmr: see Table 2.

Anal. Calcd. for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.17; H, 4.16; N, 19.39.

4,6-Dimethylpyrano[2,3-*e*]benzotriazol-8-one (**33**).

This compound was prepared from 4,6-dimethyl-7-carbethoxyamino-8-aminocoumarin (**31**) in 76% yield, mp 300° (methanol); ^{1}H nmr: see Table 2.

Anal. Calcd. for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.25; H, 4.20; N, 19.44.

Acknowledgments.

One of us (A. C.) is deeply indebted to Prodotti Formenti s.r.l., Milano, for a research grant.

REFERENCES AND NOTES

[1] To whom all correspondence should be addressed.

[2] M. P. Mullen, M. A. Pathak, J. D. West, T. J. Harrist and F. Dall'Acqua, *Nat. Cancer Inst. Monogr.*, **66**, 205 (1984).

[3] R. S. Stern, N. Laird, J. Melski, J. A. Parrish, T. B. Fitzpatrick and H. L. Bleich, *New Engl. J. Med.*, **310**, 1156 (1984).

[4] B. Bridges and G. Strauss, *Nature*, **283**, 523 (1980).

[5] G. Rodighiero, F. Dall'Acqua and M. A. Pathak, Topics in Photomedicine, K. C. S. Smith, ed, Plenum Press, New York, 1984, p 319.

[6] A. Guiotto, P. Rodighiero, G. Pastorini, P. Manzini, F. Bordin, F. Baccichetti, F. Carlassare, D. Vedaldi and F. Dall'Acqua, *Eur. J. Med. Chem.*, **16**, 489 (1981).

[7] A. Guiotto, P. Rodighiero, P. Manzini, G. Pastorini, F. Bordin, F. Baccichetti, F. Carlassare, D. Vedaldi, F. Dall'Acqua, M. Tamaro, G. Recchia and M. Cristofolini, *J. Med. Chem.*, **27**, 959 (1984).

[8] D. Averbeck, E. Moustacchi and E. Bisagni, *Biochim. Biophys. Acta*, **518**, 464 (1978).

[9] L. Dubertret, D. Averbeck, F. Zajdela, E. Bisagni, E. Moustacchi, R. Touraine and R. Latarjet, *Br. J. Dermatol.*, **101**, 379 (1978).

[10] J. Moron, C. H. Nguyen and E. Bisagni, *J. Chem. Soc., Perkin Trans. I*, 225 (1983).

[11] J. Blais, P. Vigny, J. Moron and E. Bisagni, *Photochem. Photobiol.*, **39**, 145 (1984).

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

[13] M. Palumbo, P. Rodighiero, O. Gia, A. Guiotto and S. Marciani Magno, *Photochem. Photobiol.*, **44**, 1 (1986).

[14] F. C. De Schryver, PCT Int. Appl. WO 84 02,133, June 7, 1984; *Chem. Abstr.*, **102**, 24610z (1985).

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

[16] A. Chilin, P. Rodighiero, G. Pastorini and A. Guiotto, *Gazz. Chim. Ital.*, **118**, 513 (1988).

[17] A. Guiotto, A. Chilin, G. Pastorini and M. Palumbo, *J. Heterocyclic Chem.*, **26**, 917 (1989).

[18] N. K. Gibbs, E. Quanten, S. Baydonn, C. N. Knox, R. Roelandts, F. C. De Schryver, T. G. Truscott and A. R. Young, *J. Photochem. Photobiol. B:Biology*, **2**, 109 (1988).

[19] O. Gia, S. Mobilio, A. Chilin, P. Rodighiero and M. Palumbo, *J. Photochem. Photobiol. B:Biology*, **2**, 435 (1988).

[20] F. Baccichetti, personal communication.

[21] M. A. Khan and E. C. Caldas, *Bull. Korean Chem. Soc.*, **7**, 412 (1986); *Chem. Abstr.*, **107**, 39706n (1987).

[22] K. Vara Prasad Rao and V. Sundaramurthy, *Indian J. Chem., Sect. B*, **20B**, 707 (1981).

[23] L. A. Ronald and D. E. Bliss, *J. Org. Chem.*, **43**, 1975 (1978).