Pyrrolocoumarin Derivatives as Potential Photoreagents Toward DNA

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A number of new methyl derivatives of linear and angular pyrrolocoumarins were synthesized by direct Fischer's indole synthesis. In the same way some linear 2*H*,10*H*-pyrano[2,3-*b*]carbazol-2-one and angular 2*H*,7*H*-pyrano[3,2-*c*]carbazol-2-one were prepared. The synthesis was performed starting from the 4-methyl-7-aminocoumarin and methyl groups were introduced into positions which look most promising for the photoreactivity of the compounds toward DNA.

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There are two classes of photobiological agents on which, to date, the major part of photochemical and photobiological studies have been reported: linear furocoumarins, psoralens (see for reviews [2-4]) and angular furocoumarins, angelicins [5-8].

Recently other furocoumarins with a modified annulation geometry [9] or with a different molecular arrangement, such as pyridopsoralens [10], tetrahydrobenzo- and benzofurocoumarins [11,12] are under investigation for their potential antiproliferative activity.

In addition and more recently, a new series of pyrrolocoumarins have been reported in which the nitrogen atom substitutes the oxygen atom of the furan ring of the furocoumarin nucleus [13,14]. In particular the first report [13] claims that the compounds are useful for the photochemotherapy of psoriasis, but no data were reported, and the next paper [14] reports principally the photophysical behaviour of the described pyrrolocoumarins.

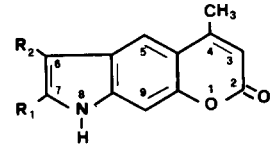
Owing to our interest for drug molecules able to photoreact with DNA and their connected biological activity, we also planned to prepare some new pyrrolocoumarins, differing from those already reported for the number and arrangement of the substituent methyl groups, *i.e.* for having methyl groups attached to the pyrrole ring. The importance, in fact, of the presence in the appropriate positions of methyl substituents is well known and it has been demonstrated that these belong to the psoralens and angelicins series [5,8].

The synthetic pathway we have followed, that is Fisher's indole synthesis directly applied to the appropriate aminocoumarin (Scheme I), is from our point of view more easy to perform with respect to the synthesis reported [13,14] which started from the preparation of indoline derivatives which were submitted to the Pechmann reaction and then dehydrogenated.

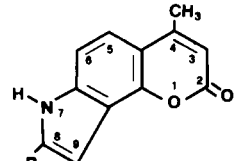
Our synthetic method allowed us to obtain contemporaneously the linear and the angular isomers, resembling the psoralen and the angelicin structures respectively. In addition we prepared the corresponding tetracyclo derivatives in which an additional cyclohexene or benzene ring is condensed to the pyrrole moiety of the molecule.

In this way the 4-methyl-7-aminocoumarin, obtained by

figure 1



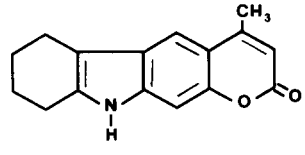
1



2

1a, 2a: $R_1 = CH_3$; $R_2 = H$

1b, 2b: $R_1 = R_2 = CH_3$



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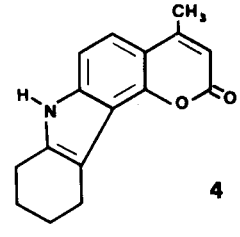

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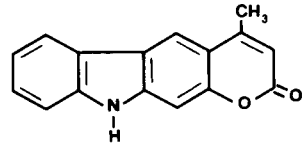

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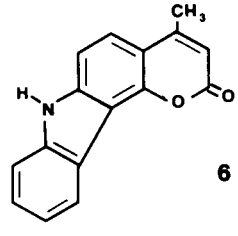
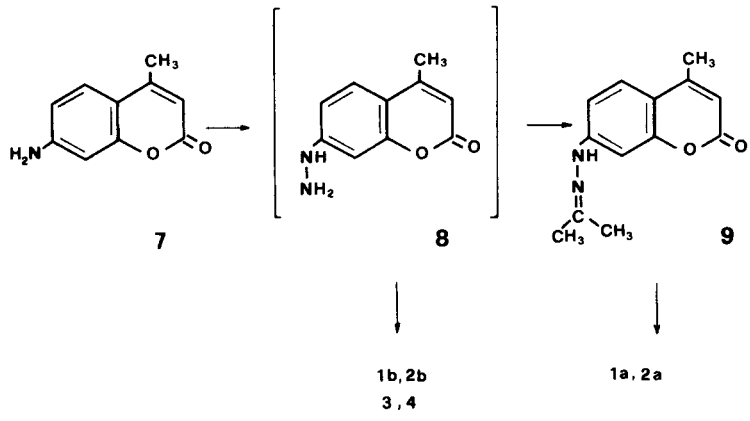


6

scheme I



the Pechmann condensation [15], was diazotized with sodium nitrite and the diazonium salt was reduced by stannous chloride [16]. The resulting mixture of coumarin-7-ylhydrazine hydrochloride and stannic chloride was directly reacted [17] with the appropriate intermediate leading to the formation of the desired compound. In the case of condensation with acetone the corresponding hydrazone was isolated and then cyclized by treatment with anhydrous zinc chloride [18].

As mentioned before, owing to the fact that the coumarin-7-ylhydrazine have both the 6 and the 8 positions free for the cyclization, the synthesis afforded, as expected, both linear (psoralen-like) and angular (angelicin-like) isomers which were separated by column chromatography.

The cyclohexenepyrrolocoumarins obtained by condensation with cyclohexanone were than dehydrogenated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) obtaining the linear and angular benzopyrrolocoumarins respectively.

In this way the following new compounds were prepared: 4,7-dimethyl-2*H*,8*H*-pyrano[3,2-*f*]indol-2-one (**1a**); 4,8-dimethyl-2*H*,7*H*-pyrano[2,3-*e*]indol-2-one (**2a**); 4,6,7-trimethyl-2*H*,8*H*-pyrano[3,2-*f*]indol-2-one (**1b**); 4,8,9-trimethyl-2*H*,7*H*-pyrano[2,3-*e*]indol-2-one (**2b**); 4-methyl-6,7,8,9-tetrahydro-2*H*,10*H*-pyrano[2,3-*b*]carbazol-2-one (**3**); 4-methyl-8,9,10,11-tetrahydro-2*H*,7*H*-pyrano[3,2-*c*]carbazol-2-one (**4**); 4-methyl-2*H*,10*H*-pyrano[2,3-*b*]carbazol-2-one (**5**); and 4-methyl-2*H*,7*H*-pyrano[3,2-*c*]carbazol-2-one (**6**).

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 chloroform methanol (95/5). Preparative column chromatography was performed using silica gel (Merck, 0.063-0.200 mm). The pmr spectra were recorded on a Varian FT-80A spectrometer with TMS as internal standard and hexadeuterioacetone as solvent, coupling constants are given in Hz; the relative peak areas and the decoupling experiments were in agreement with all assignments.

Coumarin-7-ylhydrazine (**8**).

To a solution of 1.75 g (10.0 mmoles) of 7-aminocoumarin (**7**) in 5 ml of hydrochloric acid, a solution of 0.8 g (11.0 mmoles) of sodium nitrite in 3 ml of water was added at -5° to 0°. After 30 minutes the resulting diazonium salt was poured into a cold (from -10° to -5°) solution of 5.0 g (26.0 mmoles) of stannous chloride in 5 ml of hydrochloric acid. The mixture of coumarin-7-ylhydrazine hydrochloride in hydrochloric acid (henceforth referred to as "coumarin-7-ylhydrazine") was left in the refrigerator for a minimum period of 2 hours and then directly reacted with the appropriate carbonyl compounds.

4,6,7-Trimethyl-2*H*,8*H*-pyrano[3,2-*f*]indol-2-one (**1b**) and 4,8,9-Trimethyl-2*H*,7*H*-pyrano[2,3-*e*]indol-2-one (**2b**).

A solution of coumarin-7-ylhydrazine (**8**) (10.0 mmoles) in 15 ml of acetic acid was reacted with 2-butanone (0.72 g, 10.0 mmoles) by refluxing for 1 hour. After cooling the reaction mixture was poured into 200 g of crushed ice. The crude product was filtered and the solid chromatographed on a silica gel column eluting with chloroform. From the pooled first fractions containing a single spot (tlc) the solvent was evaporated and the residue was crystallized from methanol obtaining 0.61 g (27%) of 4,8,9-trimethyl-2*H*,7*H*-pyrano[2,3-*e*]indol-2-one (**2b**), mp 238-240°; pmr: 2.37 (broad s, Me-8 or Me-9, 3H), 2.46 (d, Me-4, 3H, $J_{4Me,3}$ = 1.2), 2.52 (broad s, Me-8 or Me-9, 3H), 6.15 (q, H-3, 1H, $J_{3,4Me}$ = 1.2), 7.15 (d, H-5 or H-6, 1H, $J_{5,6}$ = 8.6), 7.23 (d, H-5 or H-6, 1H, $J_{5,6}$ = 8.6), 8.16 (broad s, N-H, 1H).

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.88; H, 5.71; N, 6.11.

From the successive fractions, containing a single compound (tlc), the solvent was evaporated and the residue was crystallized from methanol giving 0.61 g (27%) of 4,6,7-trimethyl-2*H*,8*H*-pyrano[3,2-*f*]indol-2-one (**1b**), mp 277-278°; pmr: 2.28 (q, Me-6 or Me-7, 3H, $J_{6Me,7Me}$ = 0.7), 2.40 (q, Me-6 or Me-7, 3H, $J_{6Me,7Me}$ = 0.7), 2.56 (d, Me-4, 3H, $J_{4Me,3}$ = 1.2), 6.11 (q, H-3, 1H, $J_{3,4Me}$ = 1.2), 7.11 (s, H-8, 1H), 7.79 (broad s, H-5, 1H).

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.84; H, 5.79; N, 6.05.

4,7-Dimethyl-2*H*,8*H*-pyrano[3,2-*f*]indol-2-one (**1a**) and 4,8-Dimethyl-2*H*,7*H*-pyrano[2,3-*e*]indol-2-one (**2a**).

A solution of coumarin-7-ylhydrazine (10.0 mmoles) and acetone (0.58 g, 10.0 mmoles) in 15 ml of acetic acid was refluxed for 1 hour. After

cooling the reaction mixture was poured into crushed ice obtaining a precipitate of the acetone coumarin-7-ylhydrazone (2.18 g, 95%), not crystallized, mp 235-237°; pmr: 2.04 and 2.10 (s, -N = C(Me)$_2$, 6H), 2.45 (d, Me-4, 3H, $J_{4Me,3}$ = 1.1), 6.12 (q, H-3, 1H, $J_{3,4Me}$ = 1.1), 7.03 (d, H-8, 1H, $J_{8,6}$ = 2.0), 7.16 (dd, H-6, 1H, $J_{6,5}$ = 8.8 and $J_{6,8}$ = 2.0), 7.65 (d, H-5, 1H, $J_{5,6}$ = 8.8), 9.47 (broad s, N-H, 1H).

The hydrazone (2.18 g, 9.4 mmoles) was accurately mixed with anhydrous zinc chloride (11.0 g, 80.7 mmoles) and the mixture was heated to melting (280-290°). After cooling the solid mass was suspended in water from which a precipitate was obtained which was collected and chromatographed on a silica gel column eluting with chloroform. The first fractions containing a single product (tlc) were concentrated to dryness and the residue was crystallized from methanol to afford 0.37 g (19%) of 4,8-dimethyl-2*H*,7*H*-pyrano[2,3-*e*]indol-2-one (**2a**), mp 290-292°; pmr: 2.51 (d, Me-8 and Me-4, 6H, $J_{4Me,3}$ = 1.2 and $J_{8Me,9}$ = 1.2), 6.13 (q, H-3, 1H, $J_{3,4Me}$ = 1.2), 6.53 (broad s, H-9, 1H), 7.32 (broad d, H-6, 1H, $J_{6,5}$ = 8.5), 7.38 (d, H-5, 1H, $J_{5,6}$ = 8.5).

Anal. Calcd. for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57. Found: C, 73.15; H, 5.21; N, 6.43.

From the successive fractions, containing a single compound (tlc), the solvent was evaporated and the residue crystallized from methanol giving 0.35 g (18%) of 4,7-dimethyl-2*H*,8*H*-pyrano[3,2-*f*]indol-2-one (**1a**), mp 237-239°; pmr: 2.48 (d, Me-4, 3H, $J_{4Me,3}$ = 1.1), 2.53 (d, Me-7, 3H, $J_{7Me,6}$ = 1.3), 6.13 (q, H-3, 1H, $J_{3,4Me}$ = 1.1), 6.31 (q, H-6, 1H, $J_{6,7Me}$ = 1.3), 7.23 (s, H-9, 1H), 7.85 (s, H-5, 1H).

Anal. Calcd. for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57. Found: C, 73.19; H, 5.18; N, 6.48.

4-Methyl-8,9,10,11-tetrahydro-2*H*,7*H*-pyrano[3,2-*c*]carbazol-2-one (**4**) and 4-Methyl-6,7,8,9-tetrahydro-2*H*,10*H*-pyrano[2,3-*b*]carbazol-2-one (**3**).

A solution of coumarin-7-ylhydrazine (**7**) (10.0 mmoles) in 15 ml of acetic acid was reacted with cyclohexanone (0.98 g, 10.0 mmoles) by refluxing for 1 hour. After cooling the reaction mixture was poured into 200 g of crushed ice. The crude product was filtered and the solid chromatographed on a silica gel column eluting with chloroform. From the first fractions, containing a single spot (tlc) was isolated a compound, which was crystallized from methanol to afford 0.63 g (25%) of 4-methyl-8,9,10,11-tetrahydro-2*H*,7*H*-pyrano[3,2-*c*]carbazol-2-one (**4**), mp 247-249°; pmr: from 1.80 to 1.95 (m, 9 and 10-H, 4H), 2.45 (d, Me-4, 3H, $J_{4Me,3}$ = 1.1), from 2.66 to 3.16 (m, 8 and 11-H, 4H), 6.14 (q, H-3, 1H, $J_{3,4Me}$ = 1.1), 7.18 (d, H-5 or H-6, 1H, $J_{5,6}$ = 8.6), 7.24 (d, H-5 or H-6, 1H, $J_{5,6}$ = 8.6), 8.20 (broad s, N-H, 1H).

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.76; H, 6.01; N, 5.39.

From the successive fractions, containing a single compound (tlc), the solvent was evaporated and the residue was crystallized from methanol giving 0.58 g (23%) of 4-methyl-6,7,8,9-tetrahydro-2*H*,10*H*-pyrano[2,3-*b*]-carbazol-2-one (**3**), mp 265-267°; pmr: from 1.84 to 1.99 (m, 7 and 8-H, 4H), 2.50 (d, Me-4, 3H, $J_{4Me,3}$ = 1.2), from 2.67 to 2.81 (m, 6 and 9-H, 4H), 6.15 (q, H-3, 1H, $J_{3,4Me}$ = 1.2), 7.23 (s, H-11, 1H), 7.59 (broad s, H-5, 1H).

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.76; H, 6.01; N, 5.39.

4-Methyl-2*H*,10*H*-pyrano[2,3-*b*]carbazol-2-one (**5**).

A mixture of 4-methyl-6,7,8,9-tetrahydro-2*H*,10*H*-pyrano[2,3-*b*]carbazol-2-one (**3**) (0.60 g, 23.0 mmoles) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.15 g, 52.0 mmoles) in 200 ml of toluene was refluxed for 1 hour. After cooling, the solid was filtered off and the solution was concentrated to dryness. The residue was chromatographed on silica gel column eluting with chloroform. From the pooled fractions containing a pure product (tlc), the solvent was evaporated and the residue was crystallized from methanol giving 4-methyl-2*H*,10*H*-pyrano[2,3-*b*]carbazol-2-one (**5**) (0.42 g, 70%), mp 253-255°; pmr: 2.69 (d, Me-4, 3H, $J_{4Me,3}$ = 1.2), 6.36 (q, H-3, 1H, $J_{3,4Me}$ = 1.2), from 7.35 to 7.65 (m, H-6, H-7 and H-8, 3H), 7.51 (s, H-5 or H-11, 1H), from 8.30 to 8.41 (m, H-9, 1H), 8.68 (s, H-5 or H-11, 1H), 11.72 (broad s, N-H, 1H).

Anal. Calcd. for $C_{16}H_{11}NO_2$: C, 77.09; H, 4.45; N, 5.62. Found: C, 77.02; H, 4.44, N, 5.45.

4-Methyl-2*H*,7*H*-pyrano[3,2-*c*]carbazol-2-one (**6**).

A mixture of 4-methyl-8,9,10,11-tetrahydro-2*H*,7*H*-pyrano[3,2-*c*]carbazol-2-one (**4**) (0.60 g, 23.0 mmoles) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.15 g, 52.0 mmoles) in 200 ml of toluene was refluxed for 1 hour. After cooling, the solid was filtered off and the solution was concentrated to dryness. The residue was chromatographed on silica gel column eluting with chloroform. From the pooled fractions containing a pure product (tlc), the solvent was evaporated and the residue was crystallized from methanol giving 4-methyl-2*H*,7*H*-pyrano[3,2-*c*]carbazol-2-one (**6**) (0.26 g, 45%), mp 320° dec; pmr: 2.59 (d, Me-4, 3H, $J_{4Me,3}$ = 1.2), 6.24 (q, H-3, 1H, $J_{3,4Me}$ = 1.2), from 7.40 to 7.70 (m, H-9, H-10 and H-11, 3H), 7.53 (d, H-5 or H-6, 1H, $J_{5,6}$ = 8.7), 7.79 (d, H-5 or H-6, 1H, $J_{5,6}$ = 8.7), from 8.42 to 8.53 (m, H-8, 1H).

Anal. Calcd. for $C_{16}H_{11}NO_2$: C, 77.09; H, 4.45; N, 5.62. Found: C, 77.08; H, 4.40; N, 5.45.

REFERENCES AND NOTES

[1] To whom all enquiries should be addressed.

[2] L. Musajo and G. Rodighiero, *Experientia*, **18**, 153 (1962).

[3] L. Musajo and G. Rodighiero, "Photophysiology", Vol 7, A. C. Giese, ed, Academic Press, NY and London, 1972, p 115.

[4] P. S. Song and K. J. Tapley, *Photochem. Photobiol.*, **29**, 1177 (1979).

[5] 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).

[6] F. Baccichetti, F. Bordin, F. Carlassare, F. Dall'Acqua, A. Guiotto, G. Pastorini, G. Rodighiero, P. Rodighiero and D. Vedaldi, U. S. Patent 4,312,883, Jan 26,1982; *Chem. Abstr.*, **95**, 97766b (1981).

[7] F. Dall'Acqua, D. Vedaldi, A. Guiotto, P. Rodighiero, F. Carlassare, F. Baccichetti and F. Bordin, *J. Med. Chem.*, **24**, 806 (1981).

[8] 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).

[9] P. Rodighiero, A. Chilin and A. Guiotto, *Gazz. Chim. Ital.*, **114**, 509 (1984).

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

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

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

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

[14] E. Quanten, P. Adriaens, F. C. De Schryver, R. Roelandts and H. Degreef, *Photochem. Photobiol.*, **43**, 485 (1986).

[15] R. L. Atkins and D. E. Bliss, *J. Org. Chem.*, **43**, 1975 (1978).

[16] G. T. Morgan and F. M. G. Micklethwait, *J. Chem. Soc.*, **85**, 1230 (1904).

[17] M. A. Khan and M. L. de Brito Morley, *J. Heterocyclic Chem.*, **16**, 997 (1979).

[18] E. Fischer, *Ber.*, **19**, 1563 (1886).