Methylfuroquinolinones: New Furocoumarin Isosters as Potential Photoreagents Toward DNA

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A number of methylfuro[3,2-*g*]quinolin-7(8*H*)-ones, which can be considered isosters of methylpsoralens, were synthesized. The synthesis was performed starting from the appropriate methyl quinolin-2-ones on which the methylfuran ring was condensed. The molar absorptivity at long wavelengths of these compounds is remarkably higher than that of the corresponding methylpsoralen isosters; this fact may lead to an improved photo-binding to the biological targets.

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Furocoumarins, such as 8-methoxypsoralen (8-MOP) and 5-methoxypsoralen (5-MOP), are commonly in use in the photochemotherapy (PUVA-therapy) of hyperproliferative skin diseases, such as psoriasis, micosis fungoides, etc. [2]. Although PUVA-therapy proves to be very effective, some undesiderable side effects are present such as persistent erythema, phototoxicity, possible increased risk of skin cancer [3,4] and impairment of cell-mediated immune function [5].

As these side effects are mostly attributed to psoralen-DNA cross-links rather than to monofunctional adducts [6], a line of research has emerged with the aim of obtaining furocoumarins able to behave as essentially monofunctional agents. Important derivatives include 3-carbethoxypsoralen [7,8], pyridopsoralens [9,10], benzopsoralens [11,12], angelicins [13,14] and allopsoralens [15].

Recent investigations in this field dealt with the synthesis of two series of furocoumarin isosters, namely methylpyrrolocoumarins [16,17] and methylazapsoralens [18]. They are characterized by having a pyrrole ring substituting the furan ring or a pyridine ring substituting the central benzene ring of the furocoumarin system. Pyrrolocoumarins intercalate into DNA and photobind to it monofunctionally [19,20]. Methylazapsoralens photoreact with DNA to a similar extent as 8-MOP, while their cross-linking ability is substantially reduced [21].

Both pyrrolocoumarins and azapsoralens are completely lacking of any phototoxicity in guinea pig skin [22].

Thus it appeared of interest to synthesize and investigate another series of furocoumarin isosters, methylfuroquinolinones, in which a nitrogen atom substitutes the oxygen atom of the δ-lactonic ring of furocoumarins (Figure I). These compounds can be considered the δ-lactams of *ortho*-aminocinnamic acid.

The new methylfuroquinolinones reported in this paper have a linear psoralen-like structure and contain a number of methyl substituents, since it is known from the psoralen and angelicin series that appropriately located methyl groups do enhance the ability of photoreacting with DNA.

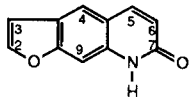


FIGURE I

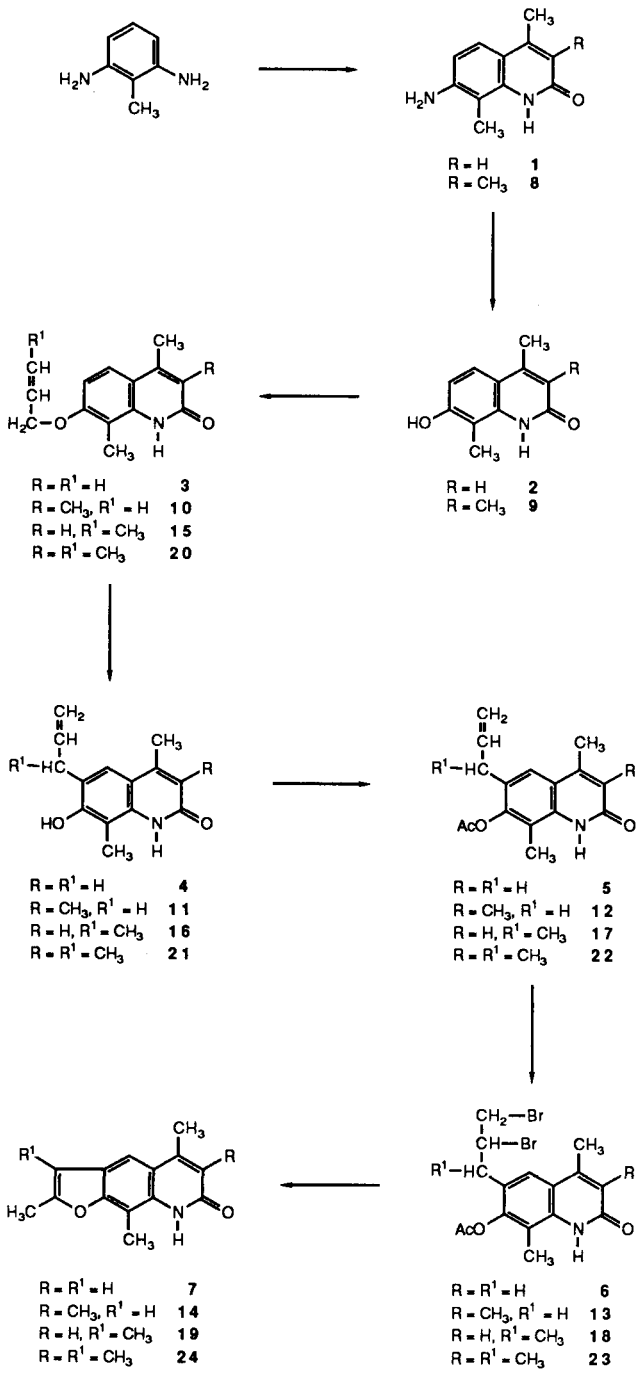
The synthesis was carried out starting from the appropriate methyl-7-hydroxyquinolin-2-ones on which the furan ring was built (see Scheme).

The required 4,8-dimethyl- and 3,4,8-trimethyl-7-hydroxyquinolin-2-ones were prepared from the corresponding 7-amino analogs. Methyl-7-aminoquinolin-2-ones were prepared by reacting 2,6-diaminotoluene with ethyl acetoacetate or ethyl methylacetoacetate. The desired products were isolated in an acceptable yield. Following the formation of the diazonium salts of the 7-amino derivatives, their hydrolysis yielded smoothly the desired methyl 7-hydroxyquinolin-2-ones. On these compounds a furan ring was condensed in a suitable way for having one or two methyl groups at the level of the furan double bond.

The key intermediate to furoquinolin-2-one derivatives, monomethylated at the furan ring, were the allylethers of the 7-hydroxyquinolinones, which were submitted to the Claisen rearrangement giving the corresponding 6-allyl derivatives. The 6-allyl derivatives were acetylated and treated with bromine at room temperature. The 2',3'-dibromopropyl derivatives were obtained and then cyclized in alkaline medium. In a similar manner derivatives carrying two methyl groups on the furan ring were prepared from 7-(1'-methylallyloxy)quinolin-2-one.

The unsubstituted furo[3,2-*g*]quinolin-7(8*H*)-one was already known. It was synthesized by an interesting method consisting, at first, in a bicycloannulation and intramolecular Diels-Alder reaction [23]. In our opinion, however, the synthetic method described in this paper is more convenient for obtaining compounds carrying methyl substituents at various positions of the furoquinolinone nucleus.

Scheme



The following new methylfuroquinolinones were accordingly obtained: 2,5,9-trimethylfuro[3,2-*g*]quinolin-7(8*H*)-one (**7**); 2,5,6,9-tetramethylfuro[3,2-*g*]quinolin-7(8*H*)-one (**14**); 2,3,5,9-tetramethylfuro[3,2-*g*]quinolin-7(8*H*)-one (**19**); and 2,3,5,6,9-pentamethylfuro[3,2-*g*]quinolin-7(8*H*)-one (**24**).

It may be expected that, as quinolin-2-one [24], also furoquinolin-2-ones exhibit lactam-lactim isomerism. Furoquinolin-2-ones are characterized in the solid state or in chloroform by a strong amide carbonyl absorption near 1650 cm^{-1}. This fact suggests that, like quinolin-2-one [24], methylfuroquinolin-2-one derivatives exist and react principally in the lactam form.

Table I

UV Spectra of Methylfuro[3,2-*g*]quinolin-7(8*H*)-ones [a]

Compound		Molar absorptivity
7	249 (max)	46500
	256 (max)	45700
	300 (max)	6100
	348 (max)	8700
	365	5600
14	250 (max)	42400
	257 (max)	41400
	302 (max)	6600
	346 (max)	10700
	365	6300
19	252 (max)	45200
	259 (max)	46500
	303 (max)	6700
	352 (max)	8300
	365	6000
24	253 (max)	40200
	259 (max)	42600
	353 (max)	11300
	365	9100

[a] Ethanol 95% solution.

The uv spectra of methylfuroquinolinones (Table I) show an absorption peak at near 350 nm; this peak presents a red shift of *ca.* 20 nm when compared to the corresponding peak of psoralens. In particular at 365 nm (the wavelength generally used to perform the photochemical and photobiological experiments), furoquinolinones show a molar absorptivity about ten times higher than psoralens. This may represent an interesting feature of this class of compounds, leading to improved photochemotherapeutic properties.

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 a chloroform-methanol mixture (95:5). 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 the internal standard and deuteriochloroform as the solvent, unless otherwise stated. Coupling constants are given in Hz; the relative peak areas and the decoupling experiments were in agreement with all assignments. The uv spectra were measured with a Perkin-Elmer 554 instrument. The ir spectra were recorded on a Perkin-Elmer 1760 FT spectrometer. All products gave satisfactory elemental analyses (within ± 0.3%).

Table II

^{1}H-nmr Spectra of Methylfuro[3,2-*g*]quinolin-7(8*H*)-one [a]

Compound	H-3	H-4	H-6	H-8	Me-2	Me-3	Me-5	Me-6	Me-9
7	6.62 q J = 1.0	7.71 s	6.45 q J = 1.1	[b]	2.63 d J = 1.0	-	2.51 d J = 1.1	-	2.68 s
14	6.39 q J = 1.1	7.62 bs	-	[b]	2.48 d J = 1.1	-	2.50 q J = 0.7	2.28 q J = 0.7	2.56 s
19	-	7.48 s	6.48 q J = 1.0	9.13 bs	2.55 bs [c]	2.18 q J = 0.9	2.40 d J = 1.0	-	2.55 bs [c]
24	-	7.49 s	-	[b]	2.40 q J = 0.8	2.18 q J = 0.8	2.53 q J = 0.8	2.28 q J = 0.8	2.54 s

[a] Deuteriochloroform. [b] Not observed. [c] Superimposed signals.

4,8-Dimethyl-7-aminoquinolin-2-one (**1**).

A mixture of 20.0 g (163.7 mmoles) of 2,6-diaminotoluene and 21.3 g (163.7 mmoles) of ethyl acetoacetate was heated at 150° in a thermostatic bath for 48 hours obtaining a dark sticky mass which solidified by treatment with a small amount of methanol (30 ml) and was collected giving a dark product. The product was purified by silica gel column chromatography by eluting with ethyl acetate. The residue obtained by evaporation of the solvent from the pooled fractions containing a single product (tlc) was recrystallized from ethanol giving 4,8-dimethyl-7-aminoquinolin-2-one (**1**) (18.8 g, 61%), mp 242° (reported [25] 243-244°); ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): 2.22 (s, Me-8, 3H), 2.42 (d, Me-4, 3H, $J_{Me-4,3}$ = 0.8), 5.63 (broadening s, -NH_2, 2H), 6.13 (q, H-3, 1H, $J_{3,Me-4}$ = 0.8), 6.70 (d, H-6, 1H, $J_{6,5}$ = 8.6), 7.40 (d, H-5, 1H, $J_{5,6}$ = 8.6), 10.30 (broadening s, -NH-CO-, 1H).

The following 7-aminoquinolin-2-one derivative was prepared in a similar manner:

3,4,8-Trimethyl-7-aminoquinolin-2-one (**8**).

This compound was prepared from 2,6-diaminotoluene and ethyl methylacetoacetate, mp 283° (ethanol, 52%); ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): 2.17 (s, Me-3, 3H), 2.23 (s, Me-8, 3H), 2.42 (s, Me-4, 3H), 5.45 (broadening s, -NH_2, 2H), 6.69 (d, H-6, 1H, $J_{6,5}$ = 8.7), 7.44 (d, H-5, 1H, $J_{5,6}$ = 8.7), 10.29 (broadening s, -NH-CO-, 1H).

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 70.98; H, 6.99; N, 13.81.

4,8-Dimethyl-7-hydroxyquinolin-2-one (**2**).

A mixture of 18.5 g (98.3 mmoles) of 4,8-dimethyl-7-aminoquinolin-2-one (**1**), 35 ml of water, 30 ml of concentrated sulphuric acid and 75 g of crushed ice was cooled to a temperature between 0° and −5°. Into this mixture, an aqueous solution (35 ml) of 9.4 g (136.2 mmoles) of sodium nitrite was added dropwise with stirring vigorously and maintaining the temperature up to 0°; when the addition was completed the mixture was stirred further for 15 minutes.

The mixture was cautiously poored into boiling 10 *M* sulphuric acid (150 ml). Boiling was continued for 10 minutes and then the mixture was diluted with water and cooled obtaining a precipitate. The precipitate was purified by silica gel column chromatography eluting with ethyl acetate. From the pooled fractions containing a single product (tlc) the solvent was evaporated and the residue was crystallized from methanol obtaining 4,8-dimethyl-7-hydroxyquinolin-2-one (**2**) (12.9 g, 70%), unmelted up to 310°; ^{1}H-nmr (tetradeuteriomethanol): 2.28 (s, Me-8, 3H), 2.46 (d, Me-4, 3H, $J_{Me-4,3}$ = 1.1), 6.30 (q, H-3, 1H, $J_{3,Me-4}$ = 1.1), 6.82 (d, H-6, 1H, $J_{6,5}$ = 9.0), 7.51 (d, H-5, 1H, $J_{5,6}$ = 9.0).

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.77; H, 5.83; N, 7.31.

The following 7-hydroxyquinolin-2-one was prepared in an analogous manner:

3,4,8-Trimethyl-7-hydroxyquinolin-2-one (**9**).

This compound was prepared from 3,4,8-trimethyl-7-aminoquinolin-2-one (**8**), mp 299° (methanol, 52%); ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): 2.20 (s, Me-3, 3H), 2.33 (s, Me-8, 3H), 2.46 (s, Me-4, 3H), 6.87 (d, H-6, 1H, $J_{6,5}$ = 8.9), 7.55 (d, H-5, 1H, $J_{5,6}$ = 8.9), 9.90 (broadening s, -NH-CO- or -OH, 1H), 10.54 (broadening s, -NH-CO- or -OH, 1H).

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89: Found: C, 70.79; H, 6.41; N, 6.83.

7-Allyloxyquinolin-2-ones **3**, **10**, **15** and **20**.

4,8-Dimethyl-7-allyloxyquinolin-2-one (**3**).

An acetone solution (2500 ml) of 9.1 g (48.1 mmoles) of 4,8-dimethyl-7-hydroxyquinolin-2-one (**2**) was reacted with 8.7 g (72.1 mmoles) of allyl bromide in the presence of anhydrous potassium carbonate (50 g). The mixture was refluxed until the starting product disappeared (tlc, 5 hours). The mixture was cooled and the potassium carbonate was filtered off. It was then washed with fresh aceton. From the filtrate and acetone washings the solvent was evaporated and the residue was crystallized from methanol giving 6.2 g (56%) of 4,8-dimethyl-7-allyloxyquinolin-2-one (**3**), mp 202°; ^{1}H-nmr: 2.30 (s, Me-8, 3H), 2.44 (d, Me-4, 3H, $J_{Me-4,3}$ = 1.0), 4.64 (dt, H-1', 2H, $J_{1',2'}$ = 4.9 and $J_{1',3'}$ = 1.4), 5.23-5.54 (m, H-3', 2H), 5.89-6.33 (m, H-2', 1H), 6.37 (q, H-3, 1H, $J_{3,Me-4}$ = 1.0), 6.82 (d, H-6, 1H, $J_{6,5}$ = 9.0), 7.49 (d, H-5, 1H, $J_{5,6}$ = 9.0), 8.80 (broadening s, -NH-CO-, 1H).

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.19; H, 6.56; N, 6.06.

The following 7-allyloxy or 7-(1'-methylallyloxy) derivatives were prepared in a similar manner:

3,4,8-Trimethyl-7-allyloxyquinolin-2-one (**10**).

This compound was prepared from 3,4,8-trimethyl-7-hydroxyquinolin-2-one (**9**), mp 230° (methanol, 60%); ^{1}H-nmr: 2.23 (s, Me-3, 3H), 2.31 (s, Me-8, 3H); 2.42 (s, Me-4, 3H), 4.63 (dt, H-1', 2H, $J_{1',2'}$ = 4.9 and $J_{1',3'}$ = 1.4), 5.20-5.55 (m, H-3', 2H), 5.86-6.27 (m, H-2', 1H), 6.81 (d, H-6, 1H, $J_{6,5}$ = 9.0), 7.51 (d, H-5, 1H, $J_{5,6}$ = 9.0), 8.85 (broadening s, -NH-CO-, 1H).

Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.92; H, 7.05; N, 5.72.

4,8-Dimethyl-7-(but-2'-enyloxy)quinolin-2-one (**15**).

This compound was prepared reacting 4,8-dimethyl-7-hydroxyquinolin-2-one (**2**) with 1-chlorobut-2-ene, mp 198° (methanol, 85%); ^{1}H-nmr: 1.76 (broadening d, H-4', 3H, $J_{4',3'}$ = 4.7), 2.31 (s, Me-8, 3H), 2.43 (d, Me-4, 3H, $J_{Me-4,3}$ = 1.1), 4.52-4.72 (m, H-1', 2H), 5.72-5.86 (m, H-2' and H-3', 2H), 6.37 (q, H-3, 1H, $J_{3,Me-4}$ = 1.1), 6.82 (d, H-6, 1H, $J_{6,5}$ = 9.0), 7.48 (d, H-5, 1H, $J_{5,6}$ = 9.0), 9.08 (broadening s, -NH-CO-, 1H).

Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.94; H, 7.06; N, 5.71.

3,4,8-Trimethyl-7-(but-2'-enyloxy)quinolin-2-one (**20**).

This compound was prepared reacting 3,4,8-trimethyl-7-hydroxyquinolin-2-one (**9**) with 1-chlorobut-2-ene, mp 215° (methanol, 30%); ^{1}H-nmr: 1.67-1.79 (m, H-4', 3H), 2.23 (s, Me-3, 3H), 2.28 (s, Me-8, 3H), 2.42 (s, Me-4, 3H), 4.52-4.62 (m, H-1', 2H), 5.72-5.85 (m, H-2' and H-3', 2H), 6.81 (d, H-6, 1H, $J_{6,5}$ = 9.1), 7.51 (d, H-5, 1H, $J_{5,6}$ = 9.1).

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.70; H, 7.41; N, 5.38.

Claisen Rearrangement to **4**, **11**, **16** and **21**.

4,8-Dimethyl-6-allyl-7-hydroxyquinolin-2-one (**4**).

A solution of 6.0 g (26.1 mmoles) of 4,8-dimethyl-7-allyloxyquinolin-2-one (**3**) in *N,N*-diethylaniline (30 ml) was refluxed for 3 hours. The reaction mixture was then cooled obtaining a precipitate which was collected, washing it many times with cyclohexane and crystallized from ethyl acetate obtaining 4.5 g (75%) of 4,8-dimethyl-6-allyl-7-hydroxyquinolin-2-one (**4**), mp 212°; ^{1}H-nmr (tetradeuteriomethanol): 2.32 (s, Me-8, 3H), 2.44 (d, Me-4, 3H, $J_{Me-4,3}$ = 1.0), 3.46 (dt, H-1', 2H, $J_{1',2'}$ = 6.3 and $J_{1',3'}$ = 1.5), 4.83-5.16 (m, H-3', 2H), 5.80-6.27 (m, H-2', 1H), 6.30 (q, H-3, 1H, $J_{3,Me-4}$ = 1.0), 7.36 (s, H-5, 1H).

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.23; H, 6.61; N, 6.08.

The following 6-allyl-7-hydroxyquinolin-2-ones or 6-(1'-methylallyl)-7-hydroxyquinolin-2-ones were prepared in an analogous manner:

3,4,8-Trimethyl-6-allyl-7-hydroxyquinolin-2-one (**11**).

This compound was prepared from 3,4,8-trimethyl-7-allyloxyquinolin-2-one (**10**), mp 175° (ethyl acetate/cyclohexane, 70%); ^{1}H-nmr (hexadeuterioacetone): 2.20 (s, Me-3, 3H), 2.51 (s, Me-4 and Me-8, 6H), 3.52-3.60 (m, H-1', 2H), 4.90-5.25 (m, H-3', 2H), 5.80-6.35 (m, H-2', 1H), 7.54 (s, H-5, 1H).

Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.88; H, 7.08; N, 5.71.

4,8-Dimethyl-6-(1'-methylallyl)-7-hydroxyquinolin-2-one (**16**).

This compound was prepared from 4,8-dimethyl-7-(but-2'-enyloxy)quinolin-2-one (**15**), mp 208° (ethyl acetate, 60%); ^{1}H-nmr (tetradeuteriomethanol): 1.46 (d, Me-1', 3H, $J_{Me-1',1'}$ = 7.0), 2.32 (s, Me-8, 3H), 2.45 (d, Me-4, 3H, $J_{Me-4,3}$ = 1.1), 3.60-3.97 (m, H-1', 1H), 5.12-5.38 (m, H-3', 2H), 5.92-6.34 (m, H-2', 1H), 6.39 (q, H-3, 1H, $J_{3,Me-4}$ = 1.1), 7.31 (s, H-5, 1H).

Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.90; H, 7.04; N, 5.73.

3,4,8-Trimethyl-6-(1'-methylallyl)-7-hydroxyquinolin-2-one (**21**).

This compound was prepared from 3,4,8-trimethyl-7-(but-2'-enyloxy)quinolin-2-one (**20**), mp 226° (methanol, 88%); ^{1}H-nmr: 1.47 (d, Me-1', 3H, $J_{Me-1',1'}$ = 7.0), 2.24 (q, Me-3, 3H, $J_{Me-3,Me-4}$ = 0.5), 2.29 (s, Me-8, 3H), 2.43 (q, Me-4, 3H, $J_{Me-4,Me-3}$ = 0.5), 3.48-3.85 (m, H-1', 1H), 5.14-5.40 (m, H-3', 2H), 5.93-6.35 (m, H-2', 1H), 7.33 (s, H-5, 1H).

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.61; H, 7.45; N, 5.40.

7-Acetoxyallylquinolin-2-ones **5**, **12**, **17** and **22**.

4,8-Dimethyl-6-allyl-7-acetoxyquinolin-2-one (**5**).

A solution of 4.3 g (18.7 mmoles) of 4,8-dimethyl-6-allyl-7-hydroxyquinolin-2-one (**4**) in 40 ml of acetic anhydride was refluxed for 1 hour in the presence of anhydrous sodium acetate. The reaction mixture was cautiously diluted with 40 ml of water, refluxed for 10 minutes and poored into water (400 ml). The precipitate was collected, washed with abundant water and crystallized from methanol to give 4.8 (95%) of 4,8-dimethyl-6-allyl-7-acetoxyquinolin-2-one (**5**) mp 239°; ^{1}H-nmr: 2.31 (s, Me-8, 3H), 2.37 (s, -$COCH_3$, 3H), 2.47 (d, Me-4, 3H, $J_{Me-4,3}$ = 1.0), 3.34 (broadening d, H-1', 2H, $J_{1',2'}$ = 6.3), 4.96-5.24 (m, H-3', 2H), 5.68-6.12 (m, H-2', 1H), 6.53 (q, H-3, 1H, $J_{3,Me-4}$ = 1.0), 7.42 (s, H-5, 1H).

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.69; H, 6.92; N, 5.16.

The following 7-acetoxy derivatives were prepared in a similar fashion:

3,4,8-Trimethyl-6-allyl-7-acetoxyquinolin-2-one (**12**).

This compound was prepared from 3,4,8-trimethyl-6-allyl-7-hydroxyquinolin-2-one (**11**) mp 264° (methanol, 77%); ^{1}H-nmr: 2.25 (s, Me-3, 3H), 2.27 (s, Me-8, 3H), 2.36 (s, -$COCH_3$, 3H), 2.43 (s, Me-4, 3H), 3.33 (broadening d, H-1', 2H, $J_{1',2'}$ = 4.0), 4.95-5.20 (m, H-3', 2H), 5.69-6.14 (m, H-2', 1H), 7.41 (s, H-5, 1H), 9.85 (broadening s, -NHCO-, 1H).

Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.38; H, 6.72; N, 4.89.

4,8-Dimethyl-6-(1'-methylallyl)-7-acetoxyquinolin-2-one (**17**).

This compound was prepared from 4,8-dimethyl-6-(1'-methylallyl)-7-hydroxyquinolin-2-one (**16**) mp 204° (methanol, 80%); ^{1}H-nmr: 1.36 (d, Me-1', 3H, $J_{Me-1',1'}$ = 7.0), 2.28 (s, Me-8, 3H), 2.37 (s, -$COCH_3$, 3H), 2.45 (d, Me-4, 3H, $J_{Me-4,3}$ = 1.1), 3.41-3.70 (m, H-1', 1H), 4.94-5.18 (m, H-3', 2H), 5.78-6.20 (m, H-2', 1H), 6.49 (q, H-3, 1H, $J_{3,Me-4}$ = 1.1), 7.39 (s, H-5, 1H), 9.99 (broadening s, -NHCO-, 1H).

Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.56, H, 6.71; N, 4.91. Found: C, 71.47; H, 6.67; N, 4.87.

3,4,8-Trimethyl-6-(1'-methylallyl)-7-acetoxyquinolin-2-one (**22**).

This compound was prepared from 3,4,8-trimethyl-6-(1'-methylallyl)-7-hydroxyquinolin-2-one (**21**) mp 235° (methanol, 83%); ^{1}H-nmr: 1.37 (d, Me-1', 3H, $J_{Me\text{-}1',1'}$ = 7.0), 2.24 (s, Me-3 and Me-8, 6H), 2.37 (s, -COCH$_3$, 3H), 2.43 (s, Me-4, 3H), 3.44-3.92 (m, H-1', 1H), 4.92-5.18 (m, H-3', 2H), 5.84-6.24 (m, H-2', 1H), 7.43 (s, H-5, 1H).

Anal. Calcd. for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.09; H, 7.06; N, 4.63.

Dibromopropylquinolin-2-ones **6**, **13**, **18** and **23**.

4,8-Dimethyl-6-(2',3'-dibromopropyl)-7-acetoxyquinolin-2-one (**6**).

An acetic solution (20 ml) containing the stoichiometric amount of bromine was added dropwise at room temperature during 20 minutes into an acetic solution (80 ml) of 4.5 g (16.6 mmoles) of 4,8-dimethyl-6-allyl-7-acetoxyquinolin-2-one (**5**). 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 5.0 g (70%) of 4,8-dimethyl-6-(2',3'-dibromopropyl)-7-acetoxyquinolin-2-one (**6**) mp 215°; ^{1}H-nmr: 2.31 (s, Me-8, 3H), 2.44 (s, -COCH$_3$, 3H), 2.52 (d, Me-4, 3H, $J_{Me\text{-}4,3}$ = 1.0), 3.54-4.00 (m, H-1' and H-3', 4H), 4.20-4.56 (m, H-2', 1H), 6.58 (q, H-3, 1H, $J_{3,Me\text{-}4}$ = 1.0), 7.57 (s, H-5, 1H).

Anal. Calcd. for $C_{16}H_{17}Br_2NO_3$: C, 44.58; H, 3.97; Br, 37.07; N, 3.25. Found: C, 44.42; H, 3.99; Br, 36.92; N, 3.20.

3,4,8-Trimethyl-6-(2',3'-dibromopropyl)-7-acetoxyquinolin-2-one (**13**).

This compound was obtained from 3,4,8-trimethyl-6-allyl-7-acetoxyquinolin-2-one (**12**) mp 240° (methanol, 75%); ^{1}H-nmr: 2.16 (s, Me-3, 3H), 2.25 (s, Me-8, 3H), 2.43 (s, Me-4, 3H), 2.46 (s, -COCH$_3$, 3H), 3.40-3.98 (m, H-1' and H-3', 4H), 4.15-4.50 (m, H-2', 1H), 7.56 (s, H-5, 1H).

Anal. Calcd. for $C_{17}H_{19}Br_2NO_3$: C, 45.87; H, 4.30; Br, 35.90; N, 3.15. Found: C, 45.80; H, 4.32; Br, 35.82; N, 3.12.

4,8-Dimethyl-6-(1'-methyl-2',3'-dibromopropyl)-7-acetoxyquinolin-2-one (**18**).

This compound was prepared from 4,8-dimethyl-6-(1'-methylallyl)-7-acetoxyquinolin-2-one (**17**) mp 216° (methanol, 92%); ^{1}H-nmr: 1.37 (d, Me-1', 3H, $J_{Me\text{-}1',1'}$ = 6.9), 2.27 (s, Me-8, 3H), 2.45 (s, -COCH$_3$, 3H), 2.48 (d, Me-4, 3H, $J_{Me\text{-}4,3}$ = 1.1), 3.59-3.93 (m, H-1' and H-3', 3H), 4.18-4.49 (m, H-2', 1H), 6.52 (q, H-3, 1H, $J_{3,Me\text{-}4}$ = 1.1), 7.54 (s, H-5, 1H), 9.80 (broadening s, -NHCO-, 1H).

Anal. Calcd. for $C_{17}H_{19}Br_2NO_3$: C, 45.87; H, 4.30; Br, 35.90; N, 3.15. Found: C, 45.76; H, 4.29; Br, 35.79; N, 3.13.

3,4,8-Trimethyl-6-(1'-methyl-2',3'-dibromopropyl)-7-acetoxyquinolin-2-one (**23**).

This compound was prepared from 3,4,8-trimethyl-6-(1'-methylallyl)-7-acetoxyquinolin-2-one (**22**) mp 225° (methanol, 90%); ^{1}H-nmr: 1.38 (d, Me-1', 3H, $J_{Me\text{-}1',1'}$ = 6.8), 2.23 (s, Me-3, 3H), 2.25 (s, Me-8, 3H), 2.44 (s, -COCH$_3$, 3H), 2.47 (s, Me-4, 3H), 3.48-3.96 (m, H-1' and H-3', 3H), 4.32-4.64 (m, H-2', 1H), 7.57 (s, H-5, 1H).

Anal. Calcd. for $C_{18}H_{21}Br_2NO_3$: C, 47.08; H, 4.61; Br, 34.80; N, 3.05. Found: C, 46.91; H, 4.60; Br, 34.69; N, 2.96.

Cyclization to **7**, **14**, **19** and **24**.

2,5,9-Trimethylfuro[3,2-*g*]quinolin-7(8*H*)-one (**7**).

To an ethanolic solution (200 ml) of 4.5 g (10.4 mmoles) of 4,8-dimethyl-6-(2',3'-dibromopropyl)-7-acetoxyquinolin-2-one (**6**) an ethanolic 4% potassium hydroxide solution was added until a molar ratio (quinoline/potassium hydroxide) 1/10 was reached. The mixture was refluxed 2 hours, chilled, diluted with twice its volume of water and acidified with diluted hydrochloric acid. A precipitate formed, which was collected. The mother liquors were concentrated at reduced pressure and extracted many times with ethyl acetate; from the dried (sodium sulphate) organic phase the solvent was evaporated obtaining a further crop of product. The pooled crude solids were crystallized from methanol giving 1.4 g (60%) of 2,5,9-trimethylfuro[3,2-*g*]quinolin-7(8*H*)-one (**7**) mp 296°; ^{1}H-nmr: see Table II.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.80; H, 5.75; N, 6.09.

The following methylfuroquinolinones were prepared by the same method:

2,5,6,9-Tetramethylfuro[3,2-*g*]quinolin-7(8*H*)-one (**14**).

This compound was prepared from 3,4,8-trimethyl-6-(2',3'-dibromopropyl)-7-acetoxyquinolin-2-one (**13**) mp 305° (methanol, 75%); ir (potassium bromide): 1650 cm^{-1} (C=O); ^{1}H-nmr: see Table II.

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.59; H, 6.31; N, 5.75.

2,3,5,9-Tetramethylfuro[3,2-*g*]quinolin-7(8*H*)-one (**19**).

This compound was prepared from 4,8-dimethyl-6-(1'-methyl-2',3'-dibromopropyl)-7-acetoxyquinolin-2-one (**18**) not melted up to 310° (methanol, 65%); ir (potassium bromide) 1646 cm^{-1} (C=O); ^{1}H-nmr: see Table II.

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.48; H, 6.23; N, 5.74.

2,3,5,6,9-Pentamethylfuro[3,2-*g*]quinolin-7(8*H*)-one (**24**).

This compound was prepared from 3,4,8-trimethyl-6-(1'-methyl-2',3'-dibromopropyl)-7-acetoxyquinolin-2-one (**23**) mp 293° (methanol, 70%); ir (potassium bromide): 1645 cm^{-1} (C=O); ^{1}H-nmr: see Table II.

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.03; H, 6.81; N, 5.41.

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