^{13}C-NMR Spectra and Carbon-Proton Coupling Constants of Variously Annulated Furocoumarins

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The ^{13}C-nmr spectra of variously annulated methylfurocoumarins are reported. The assignments of chemical shifts for all the C resonances has been achieved by using carbon-proton coupling constants, relaxation efficiency considerations and shift effects caused by the introduction of methyl groups at various positions of the furocoumarin nucleus. Substituent effects on ^{13}C chemical shifts and carbon-proton coupling constants are discussed.

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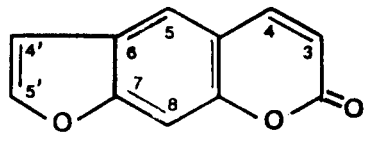
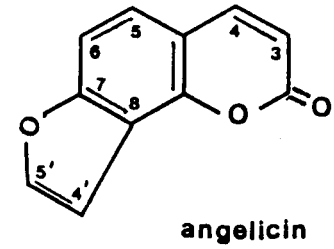
Introduction.

Until now, two classes of furocoumarins have received the majority of attention in the literature, *i.e.*, those having the linear psoralen-like structure I and those having the angular structure of angelicin II. This attention is mainly due to the interesting photobiological properties of these compounds, in conjunction with their ability to photochemically react with the DNA macromolecule [2-7]. Consequently, psoralens and angelicins have been intensively studied from every point of view and some contributions concerning the proton and carbon nmr spectroscopic properties have been published [8-13]. Among the other possibilities of annulation of the tricyclic structure of furocoumarins, only a limited number of derivatives have been prepared and of these, only the unsubstituted compounds or a few compounds carring acetyl or nitro groups as substituents have been studied photobiologically, evidencing a low photoreactivity [14-16].

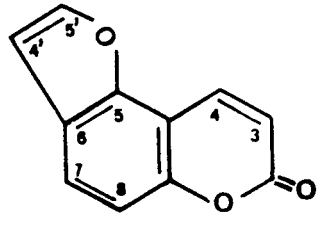
Recently, with the aim of obtaining variously annulated furocoumarins with an increased photoreactivity, as already obtained by introduction of one or more methyl groups into the psoralen [17,18] or into the angelicin molecule [5-7], we prepared a number of new methylfurocoumarins in which the furan, benzene and α-pyrone rings are angu-



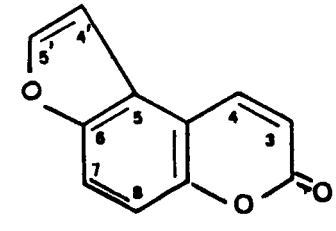
psoralen I



angelicin II



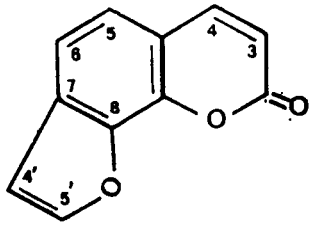
allopsoralen III



isopseudopsoralen IV

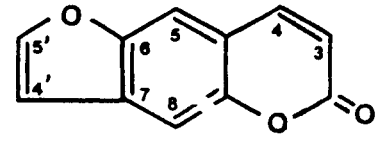
unsubstituted:	12
7,4'-dimethyl-:	16
4,5'-dimethyl-:	17
4,7-dimethyl-:	18
7,4',5'-trimethyl-:	19

7,4'-dimethyl-:	13
4,7,5'-trimethyl-:	14
4,7-dimethyl-:	15



pseudoisopsoralen V

unsubstituted:	8
5'-methyl-:	20
6,5'-dimethyl-:	7
4,6,5'-trimethyl-:	21
4,6-dimethyl-:	22
4',5'-dimethyl:	23



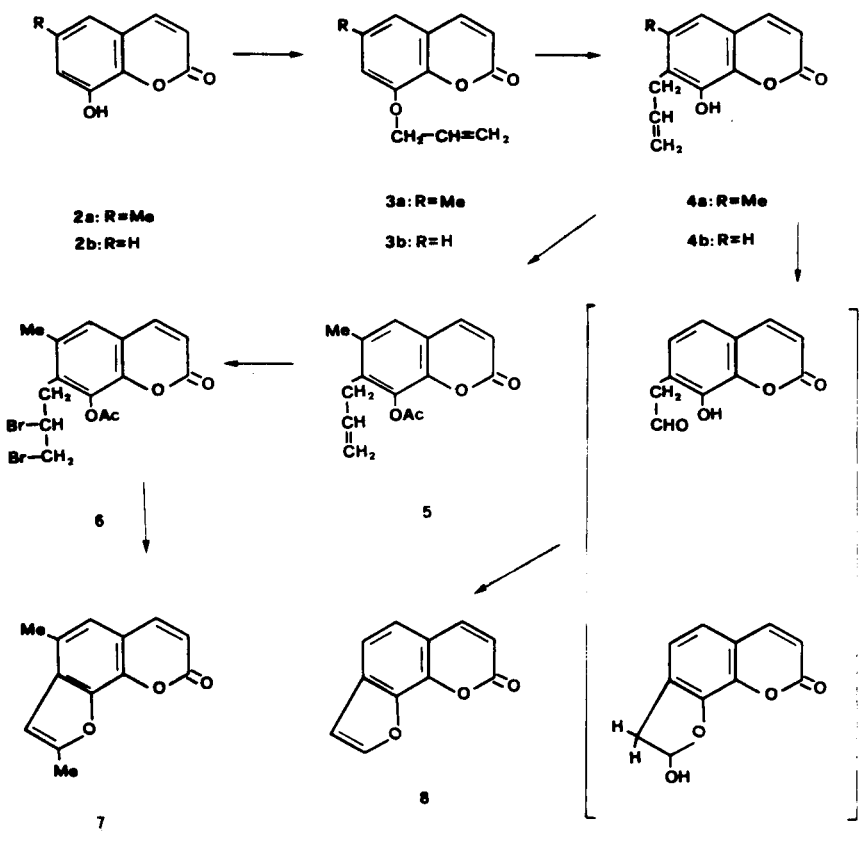
pseudopsoralen VI

4,5'-dimethyl-:	24
4',5'-dimethyl-:	25

larly annulated, with the structural arrangement of allopsoralen (III), (7*H*-furo[2,3-*f*][1]benzopyran-7-one), isopseudopsoralen (IV), (7*H*-furo[2,3-*f*][1]benzopyran-7-one) and pseudoisopsoralen (V), (8*H*-furo[3,2-*h*][1]benzopyran-8-one) [19].

Since no nmr studies describing these compounds have been reported, accompanied by the availability of various methyl substituted analogs, we were prompted to perform a ^{13}C-nmr study of these compounds; in addition, two dimethyl derivatives of pseudopsoralen (VI) (6*H*-furo[2,3-*g*]-[1]benzopyran-6-one) have also been studied.

scheme I



The unsubstituted isopseudopsoralen (IV) and pseudoisopsoralen (V), whose syntheses have already been reported [20], have now been prepared by a new synthetic pathway; in addition the synthesis of the original 6,5′-dimethylpseudoisopsoralen is also reported.

In the present work, to establish convincing attributions of chemical shifts of all the carbon atoms of the various furocoumarinic skeletons, as have already been obtained for methylangelicins [13], considerable reliance has been placed on the internal consistency of shift changes following substitutions and on the utilization of the heteronuclear coupling constant data.

Results and Discussion.

Isopseudopsoralen (**12**), pseudoisopsoralen (**8**) and 6,5′-dimethylpseudoisopsoralen (**7**) were prepared starting from 6-hydroxycoumarin (**9**), 8-hydroxycoumarin (**2b**) and the original 6-methyl-8-hydroxycoumarin (**2a**) respectively.

Condensation with allyl bromide gave the corresponding allyl ethers which were subjected to the Claisen rearrangement obtaining, by migration of the allyl group into the *ortho* position, the 5-allyl-6-hydroxycoumarin (**11**), the 7-allyl-8-hydroxycoumarin (**4b**) and the 6-methyl-7-allyl-8-hydroxycoumarin (**4a**) respectively.

For the preparation of isopseudopsoralen (**12**) and pseudoisopsoralen (**8**) (Schemes I and II), 5-allyl-6-hydroxycoumarin (**11**) and 7-allyl-8-hydroxycoumarin (**4b**) were ozonized and reduced, giving the corresponding hydroxycoumarinylacetaldehydes (mixed with their cyclic hemiacetals), which were cyclized in the presence of phosphoric acid [6]. 6,5′-Dimethylpseudoisopsoralen (**7**) was prepared according to the Kaufman procedure [21] (Scheme I); in this way the 6-methyl-7-allyl-8-hydroxycoumarin (**4a**) was acetylated, brominated and the corresponding dibromopropyl derivative was cyclized in alkaline medium, giving the desired product.

Table 1 summarizes the ^{13}C-nmr chemical shifts of the variously annulated furocoumarins obtained in a conventional proton broad band decoupled mode of acquisition; Table 2 summarizes the ^{1}H-^{13}C coupling constants, obtained by retaining the proton information through gated decoupling experiments.

Quaternary carbons can be clearly distinguished from protonated carbons by their lower signal heights, resulting from the inherently less efficient relaxation of these carbons relative to their protonated counterparts [22]. The absorption of the quaternary carbons, deriving from substitution of hydrogens by methyl groups can easily be assigned because they shift significantly downfield (Table 1). In fact, methylated C-4 carbon in the pyrone ring shows a downfield shift of *ca.* 9.0 ppm in pseudoisopsoralens and pseudopsoralens and of *ca.* 13.0 and 14.0 ppm in isopseudopsoralens and allopsoralens respectively; in these last cases, evidently,the steric interaction between the C-4 methyl group and the furan ring angularly condensed on the 5 and 6 position of the coumarin nucleus is of some importance.

Benzenoid carbons C-6 in pseudoisopsoralens and C-7 in isopseudopsoralens show a downfield shift of *ca.* 10-11 and 11-12 ppm respectively and C-4′ and C-5′ of the furan ring a downfield shift of *ca.* 11-12 ppm.

In the proton coupled spectra (Table 2) these quaternary carbon signals appear as quartets with a coupling constant of 6.0-6.5 Hz for the C-4 of the pyrone ring and for benzenoid C-6 and C-7 carbons and of 6.5-7.5 Hz for the furan ring carbons.

Carbons *ortho* to the methylated site also exhibit quartet structure with a coupling constant of 5.0-6.5 Hz, with the exception of the C-4′ signal which shows coupling of 3.0-4.0 Hz.

scheme II

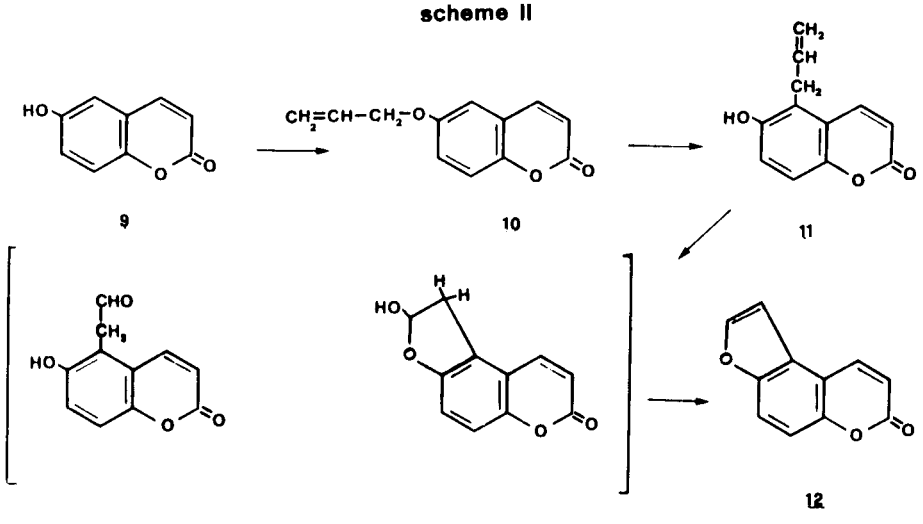


Table 1

^{13}C-NMR Spectra of Various Furocoumarins

		C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-4′	C-5′	4-Me	6-Me	7-Me	4′-Me	5′-Me
	Pseudoisopsoralen (V)																
8	Unsubstituted	159.7	114.5	144.4	122.2	116.9	131.8	141.1 [b]	140.3 [b]	115.0	107.4	147.6					
20	[a] 5′	159.8	113.6	144.5	121.9	115.9	133.5	140.4	139.5	114.1	103.5	158.8					14.0
7	6,5′	159.8	113.1	144.2	120.9	125.5	133.0	139.5	137.6	113.7	102.0	158.0		17.6			13.8
21	4,6,5′	160.1	112.6	153.6	118.0	125.5	133.3	140.5	137.8	115.1	102.3	158.4	19.4	18.3			14.2
22	4,6	160.0	113.4	153.5	118.4	126.5	131.6	141.2	138.5	116.0	106.1	147.3	19.4	18.4			
23	4′,5′	160.1	113.8	144.7	121.6	114.6	134.9	139.8	139.7	114.4	111.0	154.4				7.9	12.1
	Isopseudopsoralen (IV)																
12	Unsubstituted	161.0	116.2	140.1	124.5	151.0	114.9 [b]	113.4 [b]	151.0	111.5	104.6	147.5					
16	7,4′	161.1	114.6	139.5	123.4	150.9	126.7	113.8	151.3	110.4	116.3	143.9			15.3	10.4	
17	4,5′	161.0	114.5	153.1	125.1	151.1	114.1 [b]	112.3 [b]	150.7	112.4	103.5	158.0	22.2				14.2
18	4,7	161.3	114.0	153.1	122.6	150.8	126.7	114.5	151.2	111.3	107.5	146.5	22.2		15.4		
19	7,4′,5′	161.3	114.1	139.7	124.8	149.0	125.7	112.5	151.2	110.0	110.7	153.5			15.4	10.6 [b]	11.8 [b]
	Allopsoralen (III)																
13	7,4′	160.8	114.7	136.8	150.5	123.0	136.4	112.5	151.2	103.6	116.9	141.9			19.5	10.3	
14	4,7,5′	161.0	113.2	151.6	149.5	125.4	134.0	112.2	151.0	104.7	101.1	155.5	21.6		18.8		14.0
15	4,7	160.9	113.5	151.6	150.2	123.9	135.2	112.9	152.0	105.3	105.3	144.9	21.8		18.9		
	Pseudopsoralen (VI)																
24	4,5′	161.0	113.3	152.5	106.7	151.1	132.6	104.9	149.5	115.7	102.8	159.8	18.7				14.1
25	4′,5′	161.5	114.6	144.1	108.0	150.3	134.5	105.6	150.3	114.8	110.6	155.4				7.9	12.2

[a] The number indicate the positions of the methyl groups in the furocoumarin molecule. [b] The corresponding values may be interchanged.

Table 2

^{1}H-^{13}C Coupling Constants of Various Furocoumarins

			Isopseudopsoralen (IV)			Pseudopsoralen (VI)	
	unsubstituted **(12)**	[a] 7,4′ **(16)**	4,5′ **(17)**	4,7 **(18)**	7,4′,5′ **(19)**	4,5′ **(24)**	4′,5′ **(25)**
C-2	C2-H3 = 4.0 C2-H4 = 11.5	C2-H3 = 4.0 C2-H4 = 11.5	C2-H3 = 4.0	C2-H3 = 4.0	C2-H3 = 4.0 C2-H4 = 11.5	C2-H3 = 4.5	C2-H3 = 4.0 C2-H4 = 11.5
C-3	C3-H3 = 173.0	C3-H3 = 172.5	C3-H3 = 169.5 C3-4Me = 6.0	C3-H3 = 169.5 C3-4Me = 6.0	C3-H3 = 172.5	C3-H3 = 170.0 C3-4Me = 6.0	C3-H3 = 172.0
C-4	C4-H4 = 163.0	C4-H4 = 162.5	C4-4Me = 6.0	C4-4Me = 6.0	C4-H4 = 162.0	C4-4Me = 6.0 C4-H5 = 4.5	C4-H4 = 162.5 C4-H5 = 5.0
C-5	[b]	C5-H5′ = 6.0 C5-H4 = 4.0	C5-H7 = 4.5 C5-H4′ = 4.5	[b]	C5-H4 = 4.0	C5-H5 = 163.5	C5-H5 = 163.5 C5-H4 = 5.0
C-6	[b]	[e]	[e]	[b]	[b]	C6-H8 = 9.0 C6-H4′ = 6.5 C6-H5 = 4.0	[e]
C-7	C7-H7 = 167.0 [g]	C7-7Me = 6.0	C7-H7 = 167.0 [g]	C7-7Me = 6.5	C7-7Me = 6.5	C7-H4′ = 5.0 C7-H5 = 5.0	[b]
C-8	C8-H8 = 166.5 [g]	C8-H8 = 163.5 C8-7Me = 5.5	C8-H8 = 166.5 [g]	C8-H8 = 163.0 C8-7Me = 5.5	C8-H8 = 163.0 C8-7Me = 5.5	C8-H8 = 165.5	C8-H8 = 165.0
C-9	[b]	C9-H4 = 6.5 C9-H8 = 3.0	C9-H7 = 9.5 C9-H8 = 3.0	C9-H8 = 3.0	C9-H4 = 6.0 C9-H8 = 4.0	C9-H5 = 8.5 C9-H8 = 4.0	[e]
C-10	[b]	[b]	[b]	[b]	[e]	C10-H3 = 8.0 C10-H8 = 3.5 C10-4Me = 4.5	C10-H3 = 8.0 C10-H8 = 3.5
C-4′	C4′-H4′ = 177.5 C4′-H5′ = 13.0	C4′-H5′ = 13.0 C4′-4′Me = 6.5	C4′-H4′ = 170.5 C4′-5′Me = 4.0	C4′-H4′ = 178.0 C4′-H5′ = 13.5	C4′-4′Me = 7.0 C4′-5′Me = 4.0	C4′-H4′ = 177.0 C4′-5′Me = 3.5 C4′-H8 = 3.5	[e]
C-5′	C5′-H5′ = 203.0 C5′-H4′ = 10.0	C5′-H5′ = 200.5 C5′-4′Me = 6.5	C5′-H4′ = 10.0 C5′-5′Me = 7.0	C5′-H5′ = 203.0 C5′-H4′ = 10.0	C5′-5′Me = 7.0 C5′-4′Me = 6.5	C5′-5′Me = 7.0 C5′-H4′ = 10.0	C5′-5′Me = 7.0 C5′-4′Me = 6.5
4-Me			C-H = 128.5 4Me-H3 = 6.0	C-H = 128.5 4Me-H3 = 6.5		C-H = 128.5 4Me-H3 = 6.0	
7-Me		C-H = 129.0 7Me-H8 = 5.0		C-H = 129.0 7Me-H8 = 5.0	C-H = 128.5 7Me-H8 = 5.0		
4′-Me		C-H = 128.0			C-H = 127.5		C-H = 127.5
5′-Me			C-H = 129.0		C-H = 128.5	C-H = 129.0	C-H = 128.5

Table 2 continued

	Allopsoralen (III)					Pseudoisopsoralen (V)	
	[a] 7,4′ (13)	4,7,5′ (14)	4,7 (15)	6,5′ (7)	5′ (20)	4,6,5′ (21)	unsubstituted (8)
C-2	C2-H3 = 4.5 C2-H4 = 11.5	C2-H3 = 4.0	C2-H3 = 4.5	C2-H3 = 4.5 C2-H4 = 11.0	C2-H3 = 4.0 C2-H4 = 11.5	C2-H3 = 4.0	C2-H3 = 4.5 C2-H4 = 11.5
C-3	C3-H3 = 173.0	C3-H3 = 169.5 C3-4Me = 6.0	C3-H3 = 169.5 C3-4Me = 6.0	C3-H3 = 172.0	C3-H3 = 172.0	C3-H3 = 169.0 C3-4Me = 6.0	C3-H3 = 172.5
C-4	C4-H4 = 165.5	C4-4Me = 6.0	C4-4Me = 6.5	C4-H4 = 162.5 C4-H5 = 5.0	C4-H4 = 162.5 C4-H5 = 4.5	C4-4Me = 6.0 C4-H5 = 4.0	C4-H4 = 163.5 C4-H5 = 4.5
C-5	C5-H5′ = 8.0 C5-H4 = 3.0	C5-H4′ = 6.5	[e]	C5-H5 = 159.0 C5-6Me = 5.0 C5-H4 = 4.5	C5-H5 = 162.0 C5-H4 = 4.0	C5-H5 = 158.0 C5-6Me = 5.5	C5-H5 = 162.5 C5-H4 = 4.0
C-6	[c]	C6-H8 = 8.0 C6-7Me = 5.0 C6-H4′ = 4.0	[b]	C6-6Me = 6.0	C6-H6 = 165.0	C6-6Me = 6.0	C6-H6 = 165.5
C-7	C7-7Me = 6.0	C7-7Me = 6.5	C7-7Me = 6.5	C7-H5 = 8.5 C7-6Me = 5.0 C7-H4′ = 4.5	C7-H5 = 8.5 C7-H4′ = 4.5 doublet = 3.0 [f]	C7-H5 = 8.5 C7-6Me = 5.0 C7-H4′ = 4.5	C7-H5 = 9.0 C7-H5′ = 6.5 C7-H4′ = 4.5 doublet = 2.5 [f]
C-8	C8-H8 = 162.5 C8-7Me = 5.5	C8-H8 = 162.0 C8-7Me = 5.5	C8-H8 = 162.5 C8-7Me = 5.5	C8-H4 = 6.5 [d]	[e]	C8-H4′ = 6.5	[b]
C-9	C9-H4 = 6.0 C9-H8 = 3.5	C9-H8 = 3.0	C9-H8 = 3.5	C9-H5 = 8.5 C9-H4 = 6.0	C9-H5 = 8.5 C9-H4 = 7.0	C9-H5 = 8.5	[b]
C-10	C10-H3 = 8.0 C10-H8 = 4.0	[b]	[b]	C10-H3 = 8.0 [d]	C10-H3 = 9.0 [d] C10-H6 = 7.5 [d]	C10-H3 = 8.0 C10-4Me = 4.5 C10-H5 = 3.0	C10-H3 = 9.0 [d] C10-H6 = 7.5 [d]
C-4′	C4′-H5′ = 13.0 C4′-4′Me = 7.0	C4′-H4′ = 175.0 C4′-5′Me = 3.5	C4′-H4′ = 177.5 C4′-H5′ = 13.0	C4′-H4′ = 176.0 C4′-5′Me = 3.0	C4′-H4′ = 176.5 C4′-5′Me = 3.5 C4′-H6 = 3.5	C4′-H4′ = 176.0 C4′-5′Me = 3.0	C4′-H4′ = 178.5 C4′-H5′ = 12.5 C4′-H6 = 3.0
C-5′	C5′-H5′ = 201.5 C5′-4′Me = 6.5	C5′-H4′ = 10.0 C5′-5′Me = 7.5	C5′-H5′ = 204.0 C5′-H4′ = 10.5	C5′-H4′ = 10.5 C5′-5′Me = 7.5	C5′-H4′ = 10.5 C5′-5′Me = 7.0	C5′-H4′ = 10.0 C5′-5′Me = 7.0	C5′-H5′ = 205.0 C5′-H4′ = 11.0
4-Me			C-H = 129.0 4Me-H3 = 6.0	C-H = 129.0 4Me-H3 = 6.0			C-H = 128.5 4Me-H3 = 5.5
6-Me				C-H = 127.0 6Me-H5 = 5.0			C-H = 127.5 6Me-H5 = 5.0
7-Me	C-H = 127.5 7Me-H8 = 5.5	C-H = 127.0 7Me-H8 = 5.0	C-H = 127.5 7Me-H8 = 5.0				
4′-Me	C-H = 128.0 4′Me-H5′ = 1.5						
5′-Me		C-H = 129.0 5′Me-H4′ = 1.0		C-H = 129.0	C-H = 129.0	C-H = 129.5	

[a] The numbers indicate the position of Me substituents in the angelicin nucleus. [b] Signals not well resolved from noise. [c] Complex multiplet, structure not analyzed. [d] Broadened signals indicating the presence of unresolved coupling(s). [e] Overlapped by other signals. [f] Unassigned coupling. [g] The corresponding values may be interchanged.

In all cases the carbonyl carbon C-2 appears as a readily distinguishable sharp line absorption at the lowest field position, that is *ca.* 160.0 ppm for pseudoisopsoralens and at *ca.* 161.0 ppm for isopseudopsoralens, allopsoralens and pseudopsoralens; this signal is perturbed by the H-3 and H-4 protons with coupling constants of *ca.* 4.0 and 11.0 Hz respectively [13,23]. The chemical shift range within which this signal falls for the four classes of furocoumarins is very narrow.

The C-3 carbon signal falls at *ca.* 113.0-114.5 ppm, with the exception of isopseudopsoralens for which this signal is shifted downfield by *ca.* 1.0-2.0 ppm; in the presence of a methyl substituent at the C-4 position, the C-3 absorption appears upfield by *ca.* 1.0 ppm, except in the isopseudopsoralen for which this effect is negligible. The C-4 carbon signal appears between 144.0 and 144.5 ppm for pseudopsoralens and pseudoisopsoralens; this absorption moves upfield for isopseudopsoralens and allopsoralens, that is it appears at 139.5-140.0 ppm and *ca.* 137.0 ppm respectively.

In the furan ring the unsubstituted C-4′ carbon atom absorption appears at *ca.* 105.0-107.5 ppm; in the presence of a methyl substituent in the vicinal C-5′ position this absorption moves upfield *ca.* 2.0-4.0 ppm.

The unsubstituted C-5′ carbon atom signal appears at *ca.* 145.0-147.5 ppm and in the presence of a methyl group in the vicinal C-4′ position this signal moves upfield *ca.* 3.0 ppm.

As already observed in the angelicin series [13], when two methyl groups are present in the vicinal positions, C-4′ and C-5′, the differences between expected and observed chemical shift values for these two skeletal carbons are of relevant magnitude and it has already been suggested that this fact is due to an *ortho* steric effect [24]. The C-6 carbon atom in the pseudopsoralens and isopseudopsoralens and the C-5 in the allopsoralens, that is the carbon bearing the oxygen atom appertaining to the furan ring, shows absorptions included in a narrow chemical shift range, *i.e.* between 150.0-151.0 ppm.

However, the C-8 carbon atom in pseudoisopsoralens differs consistently, showing an absorption at *ca.* 139.5-141.0 ppm, that is 28.0-35.0 ppm downfield; this may be expected owing to the presence of the oxygen atom of the α-pyrone ring on the vicinal C-9 carbon atom.

When both the 4′ and 5′ positions of the furan ring carry a methyl substituent, the absorption of all the above-mentioned carbon atoms (C-2′ regarding the furan ring) are shifted slightly upfield, *ca.* 1.0 ppm average.

The benzenoid C-7 carbon atom of pseudoisopsoralens and pseudopsoralens, which represents the 3′-position of the condensed furan ring, shows an absorption between 131.5-133.0 ppm; in both cases this carbon atom is situated respectively *meta* to oxygen atom pertaining to the α-pyrone ring and *ortho* to the furan oxygen atom.

The C-3′ carbon atom of the furan ring in the remaining two series of furocoumarins, that is the benzenoid C-5 in isopseudopsoralen and the benzenoid C-6 in allopsoralens, shows an absorption set between 123.0 and 125.0 ppm. In the presence of two methyl groups in the furan ring, the behaviour of these last C-3′ carbon atoms differs from that of the previously mentioned C-2′ carbon atoms, in fact their absorption moves downfield *ca.* 1.0-2.0 ppm.

The absorption of the two C-9 and C-10 carbon atoms, which contemporaneously belong to the benzenic and α-pyrone rings, fall into a narrow range for the various classes of furocoumarins. In fact, the C-9 signal for isopseudopsoralens, allopsoralens and pseudopsoralens is placed at *ca.* 150.5-151.5 ppm; this signal for pseudoisopsoralens appears upfield (*ca.* 137.5-140.0 ppm) as expected because of the presence in the *ortho* position of the oxygen atom of the furan ring.

The C-10 carbon atom of pseudopsoralens and pseudoisopsoralens absorbs at *ca.* 114.0-115.0 ppm. This absorption appears shifted slightly upfield (110.0-111.0 ppm) in the cases of isopseudopsoralens, and shifted deeply upfield (103.5 ppm) for allopsoralens; in the last case, evidently, the C-10 carbon atom absorption is perturbed by the presence of the furanic ring oxygen in the *ortho* C-5 position.

In the presence of a methyl group in the vicinal 4 position of the α-pyrone ring the C-10 absorption is shifted slightly downfield by *ca.* 1.0 ppm.

The one-bond C-H couplings show quite significant differences depending on the position of the carbon atoms. In all furocoumarins not carrying methyl groups in the pyrone ring, the C3-H3 and C4-H4 interactions are quite steady at 172.0-173.0 Hz and 162.0-163.0 Hz respectively, with the exception of the C4-H4 interaction in 7,4′-dimethylallopsoralen (**13**, 165.5 Hz).

In the presence of a methyl group in the adjacent 4-position, the C3-H3 interaction drops quite consistently by *ca.* 3.0 Hz, the benzenoid ring one-bond C-H interactions are similarly quite steady among the four classes of furocoumarins: C5-H5 interaction in pseudopsoralens and pseudoisopsoralens is 162.0-163.5 Hz, the C6-H6, C7-H7 and C8-H8 interactions when they are possible, are 165.0-167.0 Hz; all these interactions drop by *ca.* 3.0 Hz, when a methyl group is present in the *ortho* position.

As previously observed for the psoralens [10] and methylangelicins [13], the largest one-bond couplings are present in the furan ring, 177.5-178.5 Hz and 203.0-205.0 Hz for C4′-H4′ and C5′-H5′ respectively; they both drop *ca.* 2.0 Hz when a methyl group is present in the vicinal position.

Two bond C-H coupling is well observable in the furan moiety, C4′-H5′ = *ca.* 13.0 Hz and C5′-H4′ = *ca.* 10.0 Hz. This interaction is well observable, even if with a minor magnitude, in the following cases where the carbon atom is linked to an oxygen atom: C2-H3 = 4.0-4.5 Hz in all cases; C9-H8 = 3.0-4.0 Hz in pseudopsoralens, allopsoralens and isopseudopsoralens and C6-H5 = 4.0 Hz in pseudopsoralens. In addition, this perturbation occurs with a magnitude of 4.0-5.0 Hz between the benzenoid carbons, which in the various annulations represent the 3′ position in the furan numbering and the proton of the 4′ position of the furan ring itself.

Other than the previously mentioned C2-H4 perturbation, the following well observable three-bond couplings have been encountered in the appropriate furocoumarins: C9-H5 = 8.5 Hz, C9-H4 = 6.0-6.5 Hz, C10-H3 = 8.0-9.0 Hz, C10-H6 = 7.5 Hz, C7-H5 = 8.5-9.0 Hz, C6-H8 = 8.0 Hz and C6-H4′ = 6.5 Hz. This interaction decreases in amplitude when it occurs through a carbon atom carrying an oxygen atom, such as C10-H8 = 3.5-4.0 Hz (pseudoisopsoralens and 7,4′-dimethylallopsoralen, **13**), C7-H5 = 5.0 Hz (4,5′-dimethylpseudopsoralen, **24**) and C5-H7 = 4.5 Hz (4,5′-dimethylisopseudopsoralen, **17**). Furthermore, three bond inter-ring couplings from C4 to H5 and C5 to H4 with a magnitude of 4.0-5.0 Hz and from C4′ to H6 with a magnitude of 3.0-3.5 Hz are also characteristically seen on those carbon signals.

The substituent methyl groups, as already reported for methylangelicins [13] and methylcoumarins [25], have chemical shifts which appear to be good indicators of their

positions. These signals in the proton coupled spectra appear as quartets with a constant of 127.5-129.0 Hz, further split by the *ortho* protons with constants of 5.0-6.5 Hz for the methyl group linked to the benzene or pyrone ring and of 1.0-1.5 Hz (when observable) for those linked to the furan ring. In addition, it can be observed that the chemical shifts of the two adjacent methyl groups in the furan ring drop by *ca.* 2.0-3.0 ppm and the methyl in the 4 position of pyrone ring is downfield shifted by *ca.* 3.0-4.0 ppm in allopsoralens and isopseudopsoralens.

EXPERIMENTAL

4,7-Dimethylallopsoralen (**15**), 7,4'-dimethylallopsoralen (**13**), 4,7,5'-trimethylallopsoralen (**14**), 7,4'-dimethylisopseudopsoralen (**16**), 7,4',5'-trimethylisopseudopsoralen (**19**), 4,6-dimethylpseudoisopsoralen (**22**), 4',5'-dimethylpseudoisopsoralen (**23**) and 4,6,5'-trimethylpseudoisopsoralen (**21**) were prepared as already described by us [19]. 4,7-Dimethylisopseudopsoralen (**18**), 4,5'-dimethylisopseudopsoralen (**17**) and 5'-methylpseudoisopsoralen (**20**) were synthesized according to Kaufman *et al.* [26-28]. 4',5'-Dimethylpseudopsoralen (**25**) was prepared according to Royer *et al.* [29] and 4,5'-dimethylpseudopsoralen (**24**) was a generous gift of Dr. M. A. Pathak, Harvard Medical School.

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 tetramethylsilane 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. The ^{13}C-nmr spectra were determined at 20 MHz with a Varian FT-80A spectrometer by using 10 mm spinning tubes; pulse width 7 μs, flip angle 30°, interpulse delay 1 s and spectral width 4,000 Hz. Saturated solutions of the samples in deuteriochloroform were prepared in order to minimize spectral accumulation times and tetramethylsilane was added as an internal standard; concentration effects, however, appeared to be of little importance.

Gated decoupling experiments which permitted the retention of nuclear Overhauser enhancement were performed for measurements on carbon-proton coupling constants. Couplings are quoted to the nearest 0.5 Hz and chemical shifts, relative to tetramethylsilane, to the nearest 0.1 ppm.

6-Methyl-8-hydroxycoumarin (**2a**).

A mixture of 4-methylpyrocatechol (**1**) (20 g, 185 mmoles), malic acid (20 g, 192 mmoles) and concentrated sulfuric acid (40 ml) was gently heated until the gas evolution had almost ceased. The reaction mixture was poured into an ice and water mixture (800 ml) and stirred vigorously until the gummy mass was completely disaggregated. The fine suspension was extracted repeatedly with ethyl acetate portions, the organic phase washed with water and dried (sodium sulfate). The crude residue obtained by evaporation of the solvent from the organic phase was chromatographed on a silica gel column eluting with chloroform. From the pooled fractions containing a single spot (tlc), the solvent was evaporated and the residue (8 g) showed (^{1}H nmr) to be constituted of two compounds, the 6-methyl-8-hydroxycoumarin (**2a**) (65%) and its isomer 5-methyl-8-hydroxycoumarin (35%). No tlc system permitted a resolution of this mixture, but repeated crystallizations of the residue from chloroform gave pure 6-methyl-8-hydroxycoumarin (**2a**) (1.3 g, 4%), mp 183-185°; ^{1}H-nmr: δ 7.65 (1H, d, J = 9.6, 4-H), δ 6.99 (1H, q, J = 2.0, 5-H or 7-H), δ 6.82 (1H, broadening s, 7-H or 5-H), δ 6.40 (1H, d, J = 9.6; 3-H) and δ 2.35 (3H, broadening s, 6-Me).

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.2; H, 4.6. Found: C, 68.1; H, 4.6.

Allyloxycoumarins.

An acetone (250 ml) solution of 6-hydroxycoumarin (**9**) [30] (5.0 g, 30.8 mmoles) was reacted with allyl bromide (5 ml, 63.0 mmoles) in the presence of anhydrous potassium carbonate (5.0 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 acetonic washings were concentrated to dryness and the residue crystallized from methanol giving the 6-allyloxycoumarin (**10**) (4.5 g, 74%), mp 92°; ^{1}H-nmr: δ 7.64 (1H, broadening d, J = 9.5, 4-H), δ 7.26 (1H, broadening d, J = 9.0, 8-H), δ 7.14 (1H, dd, J = 9.0 and J = 2.6, 7-H), δ 6.93 (1H, broadening d, J = 2.6, 5-H), δ 6.41 (1H, d, J = 9.5, 3-H), δ 6.32-5.84 (1H, m, 2'-H), δ 5.55-5.20 (2H, m, 3'-H) and δ 4.56 (2H, dt, J = 5.0 and J = 1.3, 1'-H).

Anal. Calcd. for $C_{12}H_{10}O_3$: C, 71.3; H, 5.0. Found; C, 71.4; H, 4.9.

In the same manner from 8-hydroxycoumarin (**2b**) [31] the 8-allyloxycoumarin (**3b**) was prepared (uncrystallized, 94%); ^{1}H nmr: δ 7.72 (1H, d, J = 9.6, 4-H), δ 7.37-6.84 (3H, m, 5-H, 6-H, 7-H), δ 6.39 (1H, d, J = 9.6, 3-H), δ 6.30-5.85 (1H, m, 2'-H), δ 5.57-5.20 (2H, m, 3'-H) and δ 4.66 (2H, dt, J = 5.1 and J = 1.3, 1'-H).

Anal. Calcd. for $C_{12}H_{10}O_3$: C, 71.3; H, 5.0. Found: C, 71.2; H, 5.0.

From 6-methyl-8-hydroxycoumarin (**2a**) the 6-methyl-8-allyloxycoumarin (**3a**) was prepared (uncrystallized, 95%); ^{1}H-nmr: δ 7.61 (1H, d, J = 9.5, 4-H), δ 6.89 (1H, broadening s, 5-H or 7-H), δ 6.85 (1H, broadening s, 5-H or 7-H), δ 6.39 (1H, d, J = 9.5, 3-H), δ 6.35-5.89 (1H, m, 2'-H), δ 5.59-5.19 (2H, m, 3'-H), δ 4.67 (2H, dt, J = 5.2 and J = 1.3, 1'-H) and 2.37 (3H, s, 6-Me).

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.2; H, 5.6. Found: C, 72.1; H, 5.5.

Claisen Rearrangement.

A solution of 6-allyloxycoumarin (**10**) (1.5 g, 7.5 mmoles) in *N,N*-diethylaniline (10 ml) was refluxed for 3 hours. After cooling, *n*-hexane (100 ml) was added to the mixture and the precipitate obtained was filtered and washed several times with fresh *n*-hexane. The crude product was crystallized from an ethyl acetate/cyclohexane mixture obtaining the 5-allyl-6-hydroxycoumarin (**11**) (1.14 g, 76%), mp 159°; ^{1}H-nmr (perdeuterioacetone): δ 8.60 (1H, s, 6-OH, displayed by deuterium oxide addition), δ 8.11 (1H, d, J = 9.9, 4-H), δ 7.19 and δ 7.10 (2H, two d, J = 9.0, 7-H and/or 8-H), δ 6.39 (1H, d, J = 9.9, 3-H), δ 6.30-5.78 (1H, m, 2'-H), δ 5.12-4.85 (2H, m, 3'-H) and δ 3.72 (2H, dt, J = 6.0 and J = 1.6, 1'-H).

In the same manner 8-allyloxycoumarin (**3b**) gave the 7-allyl-8-hydroxycoumarin (**4b**), mp 154° (ethyl acetate/*n*-hexane; 71%), (reported [28] 158.5-159.5°); ^{1}H-nmr (perdeuterioacetone): δ 8.77 (1H, broadening s, 8-OH, displayed by deuterium oxide addition), δ 7.90 (1H, d, J = 9.6, 4-H), δ 7.09 (2H, s, 5-H and 6-H), δ 6.34 (1H, d, J = 9.6, 3-H), δ 6.30-5.79 (1H, m, 2'-H), δ 5.24-4.94 (2H, m, 3'-H) and δ 3.52 (2H, dt, J = 6.5 and J = 1.3, 1'-H).

Anal. Calcd. for $C_{12}H_{10}O_3$: C, 71.3; H, 5.0. Found: C, 71.1; H, 5.1.

Likewise in the same manner 6-methyl-8-allyloxycoumarin (**3a**) gave 6-methyl-7-allyl-8-hydroxycoumarin (**4a**), mp 172° (ethyl acetate, 69%); ^{1}H-nmr: δ 7.64 (1H, d, J = 9.6, 4-H), δ 6.85 (1H, broadening s, 5-H), δ 6.36 (1H, d, J = 9.6, 3-H), δ 6.13 (1H, broadening s, which disappears by deuterium oxide addition, 8-OH), δ 6.18-5.70 (1H, m, 2'-H), δ 5.10-4.81 (2H, m, 3'-H), δ 3.51 (2H, dt, J = 5.9 and J = 1.4, 1'-H) and δ 2.32 (3H, broadening s, 6-Me).

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.2; H, 5.6. Found: C, 72.1; H, 5.5.

Furocoumarins Without Methyl Groups in the Furan Ring.

The 5-allyl-6-hydroxycoumarin (**11**) (1.0 g, 4.9 mmoles) was dissolved in ethyl acetate (200 ml) and into the solution, cooled in an ice bath, a current of ozonized oxygen was bubbled until 1.1 times the stoichiometric amount had been added. The solution was then submitted immediately to hydrogenation in the presence of 10% Palladium on calcium carbonate (0.3 g) and the mixture stirred until the rapid absorption of hydrogen ceased. The catalyst was removed by filtration and the solvent evaporated. To the residue 85% phosphoric acid (50 ml) was added and the mixture was heated at 100° for 20 minutes. The mixture was chilled, diluted with two volumes of water and extracted with chloroform. From the dried (sodium sulfate) organic phase the solvent was evaporated and the residue chromatographed on a silica gel column eluting with chloroform,

giving the isopseudopsoralen (**12**) (0.26 g, 28%), mp 151-152°, (methanol) (reported [14] 157°); ^{1}H-nmr: δ 7.97 (1H, dd, J = 9.6 and J = 0.6, 4-H), δ 7.79 (1H, dd, J = 2.2 and J = 0.4, 5'-H), δ 7.61 (1H, broadening dd, J = 9.0 and J = 1.0, 8-H), δ 7.21 (1H, broadening d, J = 9.0, 7-H), δ 7.01 (1H, J = 2.2 and J = 1.0, 4'-H) and δ 6.48 (1H, broadening d, J = 9.6, 3-H).

Anal. Calcd. for $C_{10}H_6O_3$: C, 71.0; H, 3.2. Found: C, 70.8; H, 3.1.

Analogously from the 7-allyl-8-hydroxycoumarin (**4b**) the pseudoisopsoralen was obtained, mp 103° (methanol, 28%) (reported [14] 109°); ^{1}H-nmr: δ 7.79 (1H, d, J = 9.6, 4-H), δ 7.77 (1H, d, J = 2.2, 5'-H), δ 7.40 and δ 7.26 (2H, two d, J = 8.2, 5-H and/or 6-H), δ 6.85 (1H, d, J = 2.2, 4'-H) and δ 6.35 (1H, d, J = 9.6, 3-H).

Anal. Calcd. for $C_{10}H_6O_3$: C, 71.0; H, 3.2. Found: C, 70.9; H, 3.1.

6,5'-Dimethylpseudoisopsoralen.

a) 6-Methyl-7-allyl-8-acetoxycoumarin (**5**).

6-Methyl-7-allyl-8-hydroxycoumarin (**4a**) (3.2 g, 14.8 mmoles) was refluxed in acetic anhydride (25 ml) containing anhydrous sodium acetate (1 g) for 1 hour. The reaction mixture was cautiously diluted with water (100 ml), refluxed for 10 minutes and poured into water (500 ml). The precipitate was collected, washed with abundant water and crystallized from methanol giving the 6-methyl-7-allyl-8-acetoxycoumarin (**5**) (2.8 g, 78%), mp 104°; ^{1}H-nmr: δ 7.62 (1H, d, J = 9.6, 4-H), δ 7.15 (1H, broadening s, 5-H), δ 6.35 (1H, d, J = 9.6, 3-H), δ 6.05-5.57 (1H, m, 2'-H), δ 5.14-4.78 (2H, m, 3'-H), δ 3.39 (2H, dt, J = 5.7 and J = 1.6, 1'-H), δ 2.41 (3H, s, 8-OAc) and δ 2.34 (3H, d, J = 0.6, 6-Me).

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.7; H, 5.5. Found: C, 69.8; H, 5.4.

b) 6-Methyl-7-(2',3'-dibromopropyl)-8-acetoxycoumarin (**6**).

Into an acetic solution (100 ml) of 6-methyl-7-allyl-8-acetoxycoumarin (**5**) (3.8 g, 11.5 mmoles) an acetic solution containing the stoichiometric amount of bromine was dropped at room temperature during a 30 minute period. After the addition was terminated the solution was stirred for a further 30 minutes. The solvent was evaporated to dryness and the residue crystallized from methanol giving the 6-methyl-7-(2',3'-dibromopropyl)-8-acetoxycoumarin (**6**) (3.2 g, 69%), mp 135°; ^{1}H-nmr: δ 7.62 (1H, d, J = 9.6, 4-H), δ 7.19 (1H, broadening s, 5-H), δ 6.37 (1H, s, J = 9.6, 3-H), δ 4.60-4.24 (1H, m, 2'-H), δ 4.04-3.53 (4H, m, 1'-H and 3'-H) and δ 2.46 (6H, s, 6-Me and 8-OAc).

Anal. Calcd. for $C_{15}H_{14}Br_2O_4$: C, 43.1; H, 3.4; Br, 38.2. Found: C, 43.0; H, 3.4; Br, 38.1.

c) Cyclization.

To an ethanolic solution (100 ml) of the 6-methyl-7-(2',3'-dibromopropyl)-8-acetoxycoumarin (**6**) (3.0 g, 7.5 mmoles) a volume of ethanolic (4%) potassium hydroxide solution was added until a molar ratio (coumarin/potassium hydroxide) 1/10 was reached. The mixture was refluxed for 80 minutes in the dark, chilled, diluted with twice its volume of water and acidified with 10% hydrochloric acid, obtaining a precipitate which was collected by filtration and crystallized from methanol to give 6,5'-dimethylpseudoisopsoralen (**7**) (0.8 g, 50%), mp 125°; ^{1}H-nmr: δ 7.70 (1H, d, J = 9.6, 4-H), δ 6.97 (1H, q, J = 0.8, 5-H), δ 6.44 (1H, q, J = 1.0, 4'-H), δ 6.30 (1H, d, J = 9.6, 3-H), δ 2.51 (3H, d, J = 1.0, 5'-Me) and δ 2.44 (3H, d, J = 0.8, 6-Me).

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.9; H, 4.7. Found: C, 72.8; H, 4.7.

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