NMR SPECTRA OF NATURAL COUMARIN DERIVATIVES

II. FUROCOUMARINS*

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We have studied the chemical shifts (CS) and coupling constants of the protons in the spectra of furocoumarins (Table 1) and have also calculated the π-electronic charges on the carbon atoms by the PPP and HMO† methods (Table 2).

The spectrum of psoralen (I) was subjected to first-order analysis; the assignment of the signals was performed on the basis of information on the π-electron densities (ED) on the carbon atoms. As in the case of the coumarins, the two doublets at 6.37 and 7.80 ppm (J = 9.6 Hz) are due to the protons in positions 3 and 4. The singlets with $\delta = 7.70$ and 7.46 ppm are due to the two para protons of the benzene nucleus. The π-electron density on C_8 is higher than on C_5 (see Table 2), and therefore the signal in the stronger field must be assigned to H_8 and that in the weaker field to H_5. The two one-proton doublets at 6.85 and 7.72 ppm with a coupling constant of 2.3 Hz correspond to the hydrogen atoms of the furan nucleus. In agreement with the results of previous investigations [4-6], the signal with $\delta = 6.85$ ppm is assigned to $H_{4'}$ and that with $\delta = 7.77$ ppm to $H_{5'}$. These results are in agreement with the ED values for $C_{4'}$ and $C_{5'}$; the HMO and PPP methods give a higher negative charge on $C_{4'}$.

The spectrum of bergapten (II) shows the features described by Reisch et al. [7]: in those cases where a coumarin has a substituent in position 5 of the molecule, the signal from H_4 is shifted downfield to 8.00 ppm and below. The results given are in agreement with this rule.

The shift mentioned is not connected with a change in the ED on C_4, but is apparently due to the anisotropic influence on H_4 of the substituents at C_5.

With the presence in bergapten of a methoxy group in position 5, the ED on C_8 increases as compared with that of psoralen (see Table 2, I), and the signal from H_8 shifts upfield by 0.36 ppm. The introduction of a methoxy group at position 8 affects H_5 in precisely the same way: in the spectrum of xanthotoxin (III) the signal from H_5 shifts upfield by 0.35 ppm. As was to be expected, here the ED on C_5 increases simultaneously (see Table 2).

The introduction of O-alkyl substituents into the benzene nucleus of a furocoumarin leads to some change in the chemical shifts of the protons of the furan nucleus which, as a rule, is accompanied by the corresponding changes in the calculated ED on the carbon atoms of the furan ring. Consequently, the ED around the corresponding nucleus is the main influence on the increase or decrease in the CSs of the ring protons. The corresponding correlation has a doubly qualitative nature: with the CSs is compared not the full ED but only the calculated ED and, moreover, in a number of cases (HMO method) the calculation is an extremely rough approximation.

*For Communication I, see [1].

†The calculations by the PPP and HMO methods were performed by means of programs kindly provided by G. I. Kagan [2] and A. V. Tutkevich (for the parameters, see [3]).

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TABLE 1. Features of the NMR Spectra of Furocoumarins*

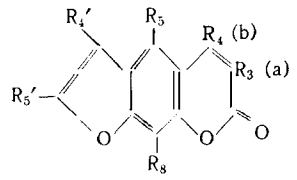
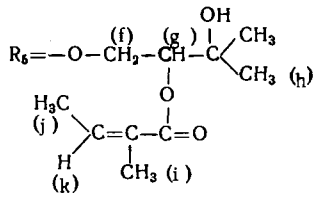
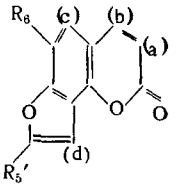
Cpd. No.	Compound	Chemical shift, δ, ppm; multiplicity,† J Hz
		
I	Psoralen	
	R_5=H(c); R_8=H(d); R_4'=H(e); R_5'=H(f);	a 6,37(d, 9,6) d 7,46(s) b 7,80(d, 9,6) e 6,85(d, 2, 3) c 7,70(s) f 7,72(d, 2, 3)
II	Bergapten	
	R_8=H(c); R_4'=H(d); R_5'=H(e); R_5=OCH_3 (f)	a 6,26(d, 10,0) d 7,02(d, 2,3) b 8,13(d, 10,0) e 7,58(d, 2,3) c 7,10(s) f 4,26(s)
III	Xanthotoxin	
	R_5=H(c); R_4'=H(d); R_5'=H(e); R_8=OCH_3(f)	a 6,35(d, 10,0) d 6,82(d, 2,3) b 7,77(d, 10,0) e 7,64(d, 2,3) c 7,35(s) f 4,28(s)
IV	Isopimpinellin	
	R_4'=H(c), R_5'=H(d); R_5=R_8=OCH_3(e)	a 6,22(d, 10,0) d 7,57(d, 2,3) b 8,04(d, 10,0) e 4,13(s) c 6,94(d, 2,3) f 4, 0(s)
V	Imperatonin	
	R_5=H(c); R_4'=H(d); R_5'=H(e); R_8=O–CH_2–CH=C(h)–CH_3 (f) (g)	a 6,17(d, 10,0) d 7,60(d, 2,3) b 7,60(d, 10,0) e 4,86(d, 6,5) c 7,20(s) g 5,49(t, 6,5) d 6,70(d, 2,3) h 1,70(s)
VI	Isoimperatonin	
	R_8=H(c); R_4'=H(d); R_5'=H(e); R_5=O–CH_2–CH=C(h)–CH_3 (f) (g)	a 6,25(d, 10,0) e 7,59(d, 2,3) b 8,14(d, 10,0) f 4,91(d, 6,1) c 7,10(s) g 5,53(t, 6,1) d 6,93(d, 2,3) h 1,70(s)
VII	Oxypeucedanin	
	R_8=H(c); R_4'=H(d); R_5'=H(e); R_5= O–CH_2–CH(f)–C(g)(O, CH_3, CH_3)(h)	a 6,27(d, 9,0) e 7,60(d, 2,5) b 8,17(d, 9,0) f 4,40(q, 11,2; 6,4) c 7,28(s) 4,62(q, 11,2; 4,6) d 6,92(d, 2,5) g 3,21(q, 4,6, 6,4) h 1,32(s) 1,39(s)
VIII	Oxypeucedanin hydrate ‡	
	R_8=H(c); R_4'=H(d); R_5'=H(e); R_5= O–CH_2–CH(f)–C(g)(OH, OH, CH_3, CH_3)(h)	a 6,19(d, 10,0) e 7,71(d, 2,5) b 8,30(d, 10,0) f 4,34(q, 10,0; 8,3) c 7,01(s) 4,75(q, 10,0; 2,3) d 7,14(d, 2,5) g 3,81(q, 8,3; 2,3) h 1,28(s) 1,32(s)
IX	Biacangelicin‡	
	R_4'=H(c); R_5'=H(d); R_5=OCH_3(e); R_8=O–CH_2–CH(f)–C(g)(OH, OH, CH_3, CH_3)(h)	a 6,29(d, 10,2) f 4,24(q, 10,3; 8,0) b 8,16(d, 10,2) 4,54(q, 10,3; 2,8) c 7,18(d, 2,5) g 3,82(d, 8,0; 2,8) d 7,80(d, 2,5) h 1,24(s) e 4,17(s) 1,28(s)

TABLE 1 (continued)

Cpd. No.	Compound	Chemical shift, δ, ppm; multiplicity, † J Hz
X	Ostruthol R_8=H (c); R_4'=H (d); R_5'=H (e) 	a 6,17 (d, 10,0) f 4,60 (q, 9,9; 7,8) b 8,00 (d, 10,0) 4,85 (q, 9,9; 3,3) c 6,98 (s) g 5,45 (q, 7,8; 3,3) d 6,95 (d, 2,5) h 1,35 (s) e 7,57 (d, 2,5) 1,39 (s) i 1,98 (wr) j 1,88 (q, 7,2; 1,5) k 6,17 (m)
XI	Peucedanin R_5=H (c); R_8=H (d) R_4'=OCH_3 (e); R_5'= $-CH(CH_3)_2$ (f, g)	a 6,44 (d, 10,0) e 4,02 (s) b 7,88 (d, 10,0) f 3,33 (m) c 7,64 (s) g 1,44 (d, 7,1) d 7,35 (s)
XII	Anhydromarmesin R_5=H (c); R_8=H (d) R_4'=H (e); R_5'=$-CH(CH_3)_2$ (f, g) 	a 6,28 (d, 10,0) e 6,35 (s) b 7,71 (d, 10,0) f 3,04 (m) c 7,46 (s) g 1,31 (d, 7,0) d 7,29 (s)
XIII	Isopsoralen R_8=H (e); R_5'=H (f)	a 6,37 (d, 10,0) e 7,39 (s) b 7,82 (d, 10,0) f 7,71 (d, 2,3) c 7,39 (s) d 7,12 (d, 2,3)
XIV	Sphondin R_8=OCH_3 (e); R_5'=H (f)	a 6,39 (d, 9,7) d 7,12 (d, 2,3) b 7,76 (d, 9,7) e 4,03 (s) c 6,77 (s) f 7,67 (d, 2,3)
XV	Oroselone R_8=H (e); R_5'= $-C(=CH_2)-CH_3$ (f, g)	a 6,36 (d, 10,0) e 7,33 (s) b 7,76 (d, 10,0) f 5,29 (wr) c 7,33 (s) 5,81 (wr) d 6,92 (s) g 2,14 (wr)
XVI	Oreselol R_8=H (e); R_5'=$-C(=CH_2)-CH_3$ (f, g)	a 6,34 (d, 10,0) d 6,92 (s) b 7,76 (d, 10,0) e 7,32 (s) c 7,37 (s) f 1,71 (s)

*The spectra were obtained on a JNM-4H-100 (100 MHz) instrument in deuterochloroform with the TMS signal taken as zero.
†d – doublet; t – triplet; q – quartet; wr – unresolved or weakly resolved signal appearing in the form of a singlet; m – multiplet.
‡Taken in CD_3OD.

TABLE 2. Effective π-Electronic Charges on the Ring Carbon Atoms in Furocoumarin Molecules

Substance No.	Compound	Method	Effective π-electronic charge						
			C_3	C_4	C_5	C_6	C_7	C_4	C_5
I	Psoralen	PPP	−0,017	−0,053	+0,025	—	−0,081	−0,076	−0,038
		HMO	−0,076	−0,087	+0,004	—	−0,087	−0,121	+0,028
II	Bergapten	PPP	−0,034	+0,046	—	—	−0,118	−0,081	−0,049
		HMO	−0,108	+0,092	—	—	−0,131	−0,114	+0,004
III	Xantho-toxin	PPP	−0,019	+0,055	−0,010	—	—	−0,077	−0,040
		HMO	−0,075	+0,087	−0,044	—	—	−0,123	+0,029
IV	Isopimp-inellin	HMO	−0,106	+0,092	—	—	—	−0,115	+0,006
XI	Peucedanin	HMO	−0,078	+0,088	+0,003	—	0,088	—	—
XIII	Isopsoralen	PPP	−0,018	+0,051	+0,008	−0,043	—	−0,080	−0,038
		HMO	−0,085	+0,087	−0,007	−0,059	—	−0,113	+0,021
XIV	Sphondin	HMO	−0,086	+0,084	−0,080	—	—	−0,114	+0,022

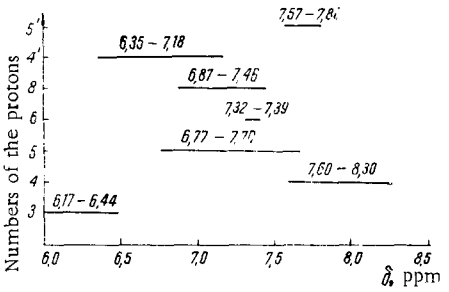


Fig. 1. Positions of the signals of the ring protons in the NMR spectra of the furocoumarins.

In the spectrum of oxypeucedanin (VII), the region of the aliphatic protons is interesting for discussion; here, in addition to the signals of the methyl groups, there are three one-proton quartets due to the protons of the —O—CH_2—CH(O)—C— fragment: the latter form an ABX system close to an AMX system. The assignment of the signals in this case can be made unambiguously on the basis of the values of the spin–spin coupling constants: the existence of a geminal constant shows that the quartets in the weaker field are due to a methylene group. The nonequivalence of the methylene protons is caused by the neighboring asymmetric carbon atom.

The signal of the methine proton is shifted upfield because it is attached to a three-membered ring. The opening of the latter leads to a paramagnetic shift of the signal of the methine proton to 3.81 ppm in the spectrum of oxypeucedanin hydrate (VIII).

The assignment given in Table 1 is also in harmony with the spectrum of ostruthol (X), in which the quartet at 3.81 ppm is shifted downfield by 1.64 ppm, which is the result of the esterification of the hydroxy group in the geminal position to the methine proton under consideration.

For biacangelicin (IX) a spectral pattern in the region of aliphatic protons similar to that for oxypeucedanin hydrate was to be expected (disregarding, of course, the appearance of the peak of a methoxy group). However, the CSs and coupling constants of the protons of the side chain of biacangelicin differ somewhat from the corresponding figures for oxypeucedanin hydrate, which is apparently due to the possibility of the formation of hydrogen bonds between the hydroxy groups of the side chain and of the coumarin nucleus.

In the ostruthol molecule there is an angelic acid residue – an angeloyl group – which is frequently found in natural coumarins. The NMR spectra of angelic acid and the isomeric tiglic acid, and also of their methyl esters, have been studied by Fraser [8], who showed the presence in them of long-range spin–spin coupling of the CH_3 protons with other protons.

The splitting of the signals of the CH_3 groups as a result of the long-range interaction is sometimes not observed directly, and a doublet and a singlet with characteristic broadening appear in the spectrum, showing the presence of an angelic acid residue in the molecule of the substance considered.

It is just this pattern which is found in the spectrum of ostruthol. The methyl group in the α position to the carboxyl gives a weakly resolved peak in the form of a broadened singlet at 1.98 ppm; the β-methyl group gives a doublet each component of which has undergone additional weak splitting. The center of the multiplet of the vinyl proton is at about 6.17 ppm.

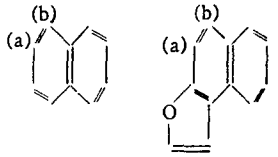
In considering the spectra of the linear furocoumarins, let us dwell on two examples of compounds with substituents in the furan nucleus. The assignments in the spectrum of peucedanin (XI) present no dif-

ficulty: in the region of aromatic protons the singlet at 7.64 ppm is due to H_5, and the singlet at 7.35 ppm to H_8. Let us start from the values of the calculated effective charges (see Table 2).

In anhydromarmesin (XII), the substituent is located at C_5'. Consequently, the protons at C_5, C_8, and C_4' give singlets. It is obvious that the signal in the weakest field must be assigned to H_5, and the peak at 7.29 ppm to H_8. In actual fact, in the peucedanin spectrum the signal from H_8 is at 7.35 ppm. It may be expected that the replacement of a methoxy group in position 4' by hydrogen will not lead to a substantial change in the CS of H_8. Furthermore, the upfield shift of the H_4' signal (6.35 ppm) in the spectrum of (XII) is completely normal, since there is an electron-donating substituent in the ortho position to this proton.

In the spectrum of the parent of the 2',3' : 7,8-furocoumarin series, isopsoralen (XIII), in place of the expected quadruplet from the protons in positions 5 and 6 a singlet appears at 7.39 ppm (7.37 ppm [9]). The charges on C_5 and C_6 (see Table 2) are −0.007 and −0.059 (HMO) and +0.008 and −0.043 (PPP), respectively. Thus, the electron densities at H_5 and H_6 will be different, and the equivalence of these protons is apparently due to the specific anisotropic influence of the furan ring in the 7,8 position.

Batterham and Lamberton [9] have considered the influence of a furan nucleus on the protons in positions 5 and 6 without determining the mechanism of this influence. By comparing the CSs of protons a and b in naphthalene (XVII) and in the naphthofuran (XVIII) they found that in the transition (XVII) → (XVIII) the signal from a shifted downfield by 0.23 ppm, and the signal from b, conversely, upfield by 0.14 ppm.



XVII XVIII

Taking into account the fact that the analogous influence of the furan nucleus is exerted on protons 5 and 6 of coumarin, these authors calculated the position of the signals from H_5 and H_6 of isopsoralen, using the data of Dharmatti et al. [10] for coumarin.* For δ_5 and δ_6 they obtained similar values of 7.49 and 7.45 ppm, which qualitatively explained the pattern observed.

The equivalence of H_5 and H_6 is retained in oroselone (XV), which has a substituent in the furan ring, and a very minute difference (0.02 ppm) is observed for δ_5 and δ_6 in the spectrum of oroselol (XVI).

The positions of the signals of the ring protons in the spectra of the furocoumarins are shown schematically in Fig. 1. It follows from this that the intervals within which the signals of the various protons appear overlap to a considerable extent, which complicates the assignment of the peaks in the spectra of compounds with unknown structures from the CS values alone. However, the use of spin–spin coupling constants may substantially simplify the problem. Thus, only the signal from H_4' can fall into the region of the signals from H_3, but if even one of the nuclei – the pyrone or the furan nucleus – has no additional substituent, the signals mentioned can easily be differentiated by means of their coupling constants. The situation is somewhat more complex with the identification of the protons of the benzene ring, but by considering the number and nature of the substituents and by using information on known compounds, it is possible as a rule, to make fairly reliable assignments.

If the influence of a number of substituents on the CSs of the ring protons is followed, some useful increments can be obtained for empirical calculations. [The CSs of the corresponding protons in psoralen (I) or in isopsoralen (XIII), depending on the type of furocoumarin for which the calculation is made, are taken as the initial values.] O-Alkyl substituents shift the signal of an ortho proton by 0.62 ppm and of a para proton by 0.41 ppm in the downfield direction, while alkyl substituents shift the signal of an ortho proton by 0.30 ppm. Finally, O-alkyl substituents in position 5, regardless of their size, shift the signal of the C_4 proton downfield by an average of 0.24 ppm and the signal from H_4' by 0.11 ppm.†

*Since Dharmatti et al. [10] performed the calculation for the spectrum in tetrahydrofuran, Batterham and Lamberton [9] introduced a correction for the influence of the solvent, which was +0.11 ppm for all the protons of the benzene ring. Bearing in mind the results of Grigg et al. [11], this method of introducing corrections must be regarded as unsatisfactory.

†All the figures given relate to solutions in $CDCl_3$ or CCl_4.

SUMMARY

The NMR spectra of a series of linear and angular furocoumarins have been studied. A series of rules of interest for structural analysis in this series of compounds has been drawn up.

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