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structural formulas of coumarin (I), psoralen (II), and isopsoralen (III)

Figure 1: structural formulas of coumarin (I), psoralen (II), and isopsoralen (III)

Abstract

Full Text

Chemistry

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NMR Spectra of Natural Coumarins and Furocoumarins

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Determining the structure of natural coumarins by chemical methods often encounters considerable difficulties. In this connection, work on the use of various physicochemical methods for this purpose, and especially NMR spectroscopy, is promising.

Dharamatti and co-workers ([1]) analyzed the proton resonance spectra of coumarin and several of its synthetic derivatives containing no more than one substituent in the benzene ring, and determined the chemical shifts and coupling constants of protons in various positions of the benzo-α-pyrone ring. Good agreement was found between the magnitudes of the proton chemical shifts and the reactivity of the various positions of the ring in electrophilic substitution reactions. In addition, it was proposed to use NMR spectra to distinguish between 3- and 4-substituted coumarins.

We have considered the NMR spectra of a series of natural coumarins and furocoumarins with the aim of using these data to determine the position of substituents in the coumarin or furocoumarin nucleus in the study of new members of this series.

The spectra were obtained on a JNM-C-60 NMR spectrometer (60 Mc). Chemical shifts in parts per million were determined relative to tetramethylsilane as an internal standard, taken as zero. Carbon tetrachloride and acetonitrile were used as solvents. In all cases spectra of saturated solutions (4–12%) were recorded. The compounds studied had literature melting points; their purity was checked by paper chromatography.

The class of compounds under study is based on the structures of coumarin (I), psoralen ($2', 3' : 7, 6$-furocoumarin) (II), and isopsoralen ($2', 3' : 7, 8$-furocoumarin) (III).

The basis for assigning the peaks was consideration of the spectra of compounds with successively substituted protons in the nucleus and the literature data for coumarin (^{1}). The experimental results obtained and the peak assignments are given in Table 1. The numbers in Table 1 correspond to the numbers in Fig. 1.

In the NMR spectrum of coumarin (Fig. 1), in addition to the readily determined quartet due to the protons in the 3- and 4-positions, there is a series of peaks belonging to the ABCD system formed by the protons of the benzene ring. In the case of substituted coumarins and furocoumarins, the picture is simplified. In herniarin (Fig. 1 II), the 5- and 6-protons form a system of the AB type; interaction between the 6- and 8-protons is practically absent. Accordingly, the doublets with $\delta = 7.20$ and 6.37, $J = 10$ cps, must be assigned

to the 5- and 6-protons, while the singlet with $\delta = 6.73$ to the proton in position 8. In scopoletin (III) the 5- and 8-protons give two singlets, 7.05 and 6.90 ppm, respectively. In the present case, as in the preceding one, the signal in the weaker field is assigned to the 5-proton, and that in the stronger field to 8. Such an assignment is understandable if one takes into account that, as a result of conjugation with the $C = O$ group of the α-pyrone ring, the electron density in the 5-position is lower than in 8 [2].

The same is also true for the 6-position, in which the electron density is higher than in 5 and 7. Therefore the assignments in the spectrum of osthol (IV) are made quite simply: the doublets with $\delta = 7.16$ and 6.78, $J = 9$ Hz, are assigned to the 5- and 6-protons, respectively. A somewhat more complicated picture is observed in the spectrum of psoralen (V). Here, in addition to the two doublets belonging to the 3- and 4-protons, one should expect two further doublets due to the two interacting protons in the $4'$- and $5'$-positions, and two singlets from the 5- and 8-protons. In the spectrum obtained, because of overlapping signals the picture observed is not so clear; however, the assignments can be made quite definitely. The doublet at 6.93 ppm, $J = 2$ Hz, is due to the proton in position $4'$; the same splitting can be observed for the signal with $\delta = 7.82$. It may therefore be assigned to the proton in position $5'$. Practically at the same place lies the peak of the 5-proton ($\delta = 7.80$). Finally, the singlet at 7.45 ppm is assigned to the proton in the 8-position. On the basis of these assignments, all the remaining spectra of substituted furocoumarins can also be unambiguously interpreted. In doing so, the influence of substituents on the magnitude of the chemical shift for the different protons must be taken into account. Thus, for example, in the spectrum of xanthotoxin (VI) the signal from the 5-proton lies in the same region as the signal from the 8-proton in the spectrum of psoralen (V).

Fig. 1. NMR spectra of natural coumarins and furocoumarins in the 5.5–8 ppm region. The numbers in the figure denote the positions of the protons responsible for the appearance of the given peaks. The names of the compounds are given in Table 1. The spectrum of coumarin (I) in CCl_4 is shown.

Such a diamagnetic shift of the signal from the 5-proton in the spectrum of

Fig. 1. NMR spectra of natural coumarins and furocoumarins in the 5.5–8 ppm region. The numbers in the figure denote the positions of the protons responsible for the appearance of the given peaks. The names of the compounds are given in Table 1. The spectrum of coumarin (I) in CCl_4 is shown.

Figure 2: Fig. 1. NMR spectra of natural coumarins and furocoumarins in the 5.5–8 ppm region. The numbers in the figure denote the positions of the protons responsible for the appearance of the given peaks. The names of the compounds are given in Table 1. The spectrum of coumarin (I) in CCl_4 is shown.

xanthotoxin is due to the electron-donating influence of the methoxy group in the 8-position.

Analysis of the experimental data makes it possible to draw certain conclusions concerning the distribution of electron density in coumarin and furocoumarin molecules, the influence of substituents on this distribution, and also the applicability of the NMR method for identifying different types of substitution in the series of compounds studied.

Table 1

No.	Compound	Solvent	δ_3	δ_4	δ_5	δ_6	δ_7	δ_8	$\delta_{4'}$	$\delta_{5'}$	J_{34}	J_{56}	$J_{4'5'}$
I	Coumarin; $R_5 = R_6 = R_7 = R_8 = H$	Tetrahydrofuran	6.43	7.91	7.74	7.33	7.56	7.31	–	–	9.8	8.5	–
I	Coumarin; $R_5 = R_6 = R_7 = R_8 = H$	Acetonitrile	6.40	7.80	–	–	–	–	–	–	10	–	–
I	Coumarin; $R_5 = R_6 = R_7 = R_8 = H$	CCl_4	6.32	7.68	–	–	–	–	–	–	10	–	–

No.	Compound	Solvent	δ_3	δ_4	δ_5	δ_6	δ_7	δ_8	$\delta_{4'}$	$\delta_{5'}$	J_{34}	J_{56}	$J_{4'5'}$
II	Terniarin; $R_5 = R_6 = R_8 = H; R_7 = OCH_3$	CCl_4	6.07	7.45	7.20	6.73	–	6.73	–	–	10	10	–
III	Skoparon; $R_5 = R_8 = H; R_6 = R_7 = OCH_3$	Acetonitrile	6.12	7.72	7.05	–	–	6.90	–	–	10	–	–
IV	Osthol; $R_5 = R_6 = H; R_7 = OCH_3; H_8 = CH_2-CH = C(CH_3)_2$	CCl_4	6.02	7.45	7.16	6.78	–	–	–	–	9	9	–
V	Psoralen; $R_{5'} = R_{4'} = R_5 = R_8 = H$	Acetonitrile	6.31	7.93	7.80	–	–	7.45	6.93	7.82	10	–	2
VI	Xanthotoxin; $R_5 = R_{4'} = R_{5'} = H; R_8 = OCH_3$	»	6.30	7.90	7.46	–	–	–	6.91	7.83	10	–	2
VII	Isopimpinellin; $R_{4'} = R_{5'} = H; R_5 = R_8 = OCH_3$	»	6.22	8.10	–	–	–	–	7.12	7.75	10	–	2

No.	Compound	Solvent	δ_3	δ_4	δ_5	δ_6	δ_7	δ_8	$\delta_{4'}$	$\delta_{5'}$	J_{34}	J_{56}	$J_{4'5'}$
VIII	Imperatorin; $R_5 = R_{5'} = R_{4'} = H$; $R_{4'} = O-CH_2-CH = C(CH_3)_2$	CCl_4	6.17	7.60	7.20	–	–	–	6.70	7.60	10	–	2
XI	Isoimperatorin; $R_{5'} = R_8 = R_{3'} = H$; $R_5 = O-CH_2-CH = C(CH_3)_2$	›	6.16	8.05	–	–	–	7.07	6.87	8.05	10	–	2
X	Anhydropeucedanin; $R_{4'} = R_5 = R_8 = H$; $R_{5'} = CH(CH_3)_2$	Acetone	6.30	7.90	7.66	–	–	7.37	6.53	–	10	–	–
XI	Peucedanin; $R_5 = R_8 = H$; $R_{4'} = OCH_3$; $R_{5'} = CH(CH_3)_2$	›	6.30	7.81	7.68	–	–	7.25	–	–	10	–	–
XII	Isopsoralen	›	6.24	7.89	7.43	7.43	–	–	7.07	7.77	10	–	2

Comparison of the position of the benzene signal (in tetrahydrofuran) with the positions of the proton peaks of the benzene nucleus for coumarin (I) shows that the signals from H_5 and H_7 undergo a considerable paramagnetic shift ($\Delta\delta_5 = +0.58$ ppm; $\Delta\delta_7 = +0.40$ ppm), whereas condensation has a smaller effect on the 6- and 8-protons ($\Delta\delta_6 = +0.17$ ppm; $\Delta\delta_8 = +0.15$ ppm). This is consistent with a number of chemical and spectral data ($^{2-4}$), according to which the 5- and 7-positions are conjugated with the carbonyl-

group of the α-pyrone ring to a much greater extent than 6 and 8. The same conclusion follows from consideration of the effect of substituents on the chemical shift of H_3 and H_4. Thus, introduction of a methoxyl group into the 7-position of coumarin (herniarin) shifts the signals of the 3- and 4-protons into the region of stronger field by 0.25 and 0.23 ppm, respectively. At the same time, introduction of a second methoxy group into the 6-position (scoparone) and of a γ, γ-dimethylallyl group into the 8-position (osthol) does not lead to a further increase in the shielding of H_3 and H_4, despite the electron-donor character of the groups introduced.

Upon condensation of coumarin with a furan ring, the signal from H_3 also undergoes a diamagnetic shift (0.09 ppm), but to a smaller extent than upon introduction of a methoxy group into the 7-position. At the same time, there is a considerable paramagnetic shift of the signals from $H_{4'}$ and $H_{5'}$ in comparison with their positions for the furan molecule ($\Delta\delta_{4'} = +0.63$ ppm; $\Delta\delta_{5'} = +0.45$ ppm). Such a shift may be due both to an increase in the degree of delocalization of the mobile electrons in the closed system of the furocoumarin ring as compared with the furan ring and, consequently, to an enhancement of the ring current, and to the electron-acceptor effect of the pyrone $C = O$ group. These data are in agreement with the values of the integral intensities of the $C = O$ bands in the IR spectra, which increase on going from 5,6-dimethyl-α-pyrone to coumarin and from coumarin to furocoumarin by 0.8 and 0.4 practical unit, respectively (^{5},^{6}).

From consideration of the data in Table 1 and the spectra presented for the compounds studied, it may also be concluded that each of the substitution types considered is characterized by definite values of chemical shifts and spin-spin coupling constants, sufficiently characteristic for their identification. Thus, NMR spectra make it possible to distinguish 7-monosubstituted, 6,7- and 7,8-disubstituted coumarins, 5-, 8-, 4′- and 5′-monosubstituted furocoumarins, and their corresponding disubstituted derivatives. The determined chemical shifts and coupling constants may make it possible to identify also those types of substituted compounds representatives of which were not at our disposal.

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Note: Figure translations are in progress. See original paper for figures.