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^{13}C NMR SPECTRA OF 3- AND 5-SUBSTITUTED FLAVONE DERIVATIVES

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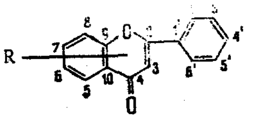
In a study of the acid–base characteristics of flavone compounds [1-3] a number of features of the behavior of compounds with the 3- and 5- models of substitution have been detected the reason for which consists in the specific natures of their electronic and geometrical structures [4, 5].

In view of the fact that changes in the ^{13}C chemical shifts agree semiquantitatively with changes in the electron densities on the corresponding carbon atoms under the influence of substituents in an aromatic system [6, 7], we have studied the ^{13}C NMR spectra of the compounds of interest to us in order to obtain information on their electronic structures.

In the present work we have considered the ^{13}C spectra of 3-hydroxyflavone (II), 3-methoxyflavone (III), 5-hydroxyflavone (IV), and 5-methoxyflavone (V) and have identified all the signals (Table 1)



I. $R = H$
II. $R = 3\text{-OH}$
III. $R = 3\text{-OCH}_3$
IV. $R = 5\text{-OH}$
V. $R = 5\text{-OCH}_3$

The assignment of the signals was based on the results obtained both from high-resolution ^{13}C NMR spectra and from spectra with the broad-band suppression of spin–spin coupling with ^{1}H nuclei.

The procedure for the interpretation of the spectra has been explained for, as an example, the case of 3-hydroxyflavone, the ^{13}C NMR spectrum of which is shown in Fig. 1. Under the conditions of broad-band decoupling from the protons, the signals corresponding to the pairs of equivalent carbon atoms C-2', 6', and C-3', 5' of the aromatic ring B (127.63 and 128.46 ppm) are distinguished from the signals of the other ^{13}C nuclei having directly attached protons by their approximately doubled intensity. Their relative assignment is simple, since the $^{13}C-^{1}H$ constants through three bonds in the benzene ring are always considerably greater in absolute magnitude than through two or four bonds [10] and have values of the order of 6-10 Hz. The signal with δ 127.63 ppm appears in the high-resolution spectrum as a doublet of triplets ($^1J_{CH}$ 163.2 Hz; $^3J_{CH}$ 6.6 Hz), i.e., it can be assigned to the C-2',6' atoms, each of which has two protons attached to the meta carbon atoms (C-4',6' and C-2',4', respectively).

The signal with δ 128.46 ppm is a doublet of doublets ($^1J_{CH}$ 162.1 Hz, $^3J_{CH}$ 6.2 Hz) with a small additional splitting of the components, i.e., it corresponds to the C-3',5' carbon atoms. In the high-resolu-

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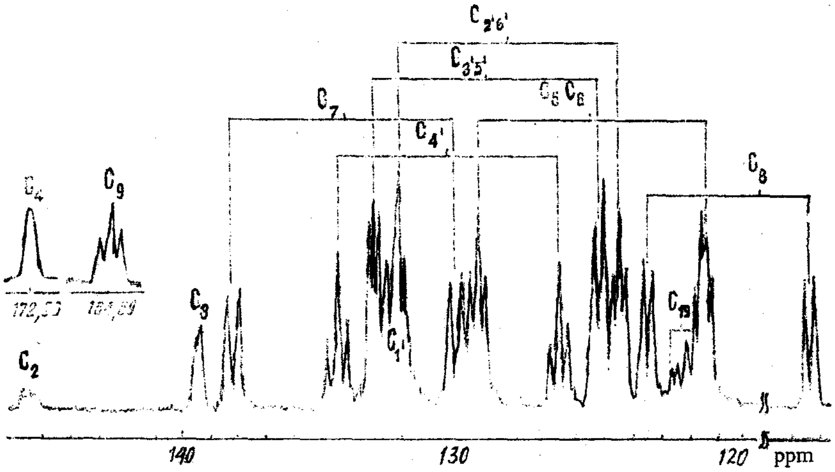

Fig. 1. High-resolution ^{13}C NMR spectrum of 3-hydroxyflavone (the positions of the signals are given in ppm from TMS).

tion spectrum, the C-4' signal forms a doublet of symmetrical triplets (δ 129.82 ppm, $^1J_{CH}$ 161.8 Hz, $^3J_{CH}$ 7.5 Hz), which distinguishes it from the signals of all the other carbon atoms having a directly attached proton.

The signals of the carbon atoms with no protons attached can easily be identified both from the absence of direct $^1J_{CH}$ constants for them in the high-resolution spectrum and by their appreciably lower intensity in the $^{13}C\{^1H\}$ spectrum. The latter is due to their greater relaxation time T_1 and the decrease in the Overhauser effect for them. Among signals of these carbon atoms (C-1',-2,-3,-4,-9,-10), the assignment of the C-4 carbonyl carbon causes no difficulties in view of the substantially greater value of its chemical shift (172.96 ppm). Apart from C-4, the C-9, C-2, and C-3 nuclei, to which electronegative oxygen atoms are directly attached, shifting the signal of the neighboring sp^2 C atom downfield by 20-30 ppm, show the greatest descreening effect.

The signal of the C-9 carbon atom, which has two meta protons appears in the high-resolution spectrum in the form of a triplet (δ 154.59 ppm, $^3J_{CH} \approx 8$ Hz). The other two descreened carbon atoms can be identified from the widths of their signals in the high-resolution ^{13}C NMR spectrum, since, because of interaction with the protons of ring B,C-2 has a considerably greater line width when its structure is not resolved (δ 145.2 ppm) than C-3 (δ 139.03 ppm).

The C-10 atom has an oxygen substituent in the ortho position (at C-9), which leads to an increase in the screening of C-10 by 10-15 ppm, i.e., its signal is to be expected in the strongest field (121.28 ppm). In the high-resolution spectrum the signal has the form of a quartet with J_{CH} 9.8 and 4.5 Hz, apparently through interaction with H-6 and H-8, respectively. For C-1' (δ 131.29 ppm), the fine structure of the signal of which is masked by overlapping with the C-3',5' components, such multiplicity cannot be detected. The C-1' signal should appear in the spectrum in the form of a symmetrical triplet because of interaction with H-3' and H-5', as is observed in the spectra of other monosubstituted flavones.

The C-5, -6, -7, and -8 signals cannot be identified from the nature of their multiplicities, since each of them appears in the spectrum in the form of a doublet of doublets because of the direct attachment of the proton and the presence of a proton on a meta carbon atom. The quartet shifted upfield to the greatest extent (δ 118.34 ppm, $^1J_{CH}$ 166 Hz, $^3J_{CH}$ 7.3 Hz) can be assigned to C-8, since, because of the ether oxygen in the ortho position the screening of this atom must be 10-15 ppm greater than for benzene. The meta-ketone fragment does not in fact have an influence on the screening of C-8. Conversely, the C-7 signal is descreened to the greatest extent, which is due to the influence of the CO group in the para position with a very slight contribution to the screening of this carbon atom from the meta ether group (δ_{C-7} 133.65 ppm, $^1J_{CH}$ 164 Hz, $^3J_{CH}$ 8.6 I The C-5 and C-6 multiplets are fairly close to one another (δ 124.75 and 125.50 ppm), and it is impossible to assign them unambiguously.

A similar procedure was used in the analysis of the spectra of compounds (III-V). The results obtained (see Table 1) are in good agreement with the values of the ^{13}C chemical shifts known for flavone itself [8] and for some its derivatives [9].

TABLE 1. ^{13}C Chemical Shifts of Flavone (ppm from TMS Internal)

Compound	R	Number of the carbon atom													
		2	3	4	5	6	7	8	9	10	1′	2′, 6′	3′, 5	4′	CH_3O
I	H*	163,0	107,3	178,0	125,4	124,9	133,5	117,9	156,0	123,7	131,5	126,0	128,8	131,3	—
II	3–OH	145,20	139,03	172,96	124,75	124,50	133,65	118,34	154,59	121,28	131,29	127,63	128,46	129,82	—
III	3–OCH_3	147,03	140,86	167,11	124,95	124,98	134,02	118,39	154,74	123,54	130,46	128,24	128,63	130,83	59,66
IV	5–OH	164,26	105,75	183,32	156,03	111,09	136,08	107,64	159,93	110,23	130,64	126,69	129,27	132,41	—
V	5–OCH_3†	160,6	108,7	177,8	159,4	109,8	133,4	106,2	157,9	≈114,0	131,9	125,6	128,6	131,0	56,3
V	5–OCH_3	160,01	108,39	176,39	159,11	109,96	134,21	107,26	157,56	113,83	130,85	126,0	129,0	131,44	56,09

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*Literature information [8] (solution in $CDCl_3$).

†Literautre information [9] (solution in $CDCl_3$).

TABLE 2. Changes in the Chemical Shifts (Δδ*, ppm) in (II)-(V) Relative to Unsubstituted Flavone

Compound	Number of the carbon atom											
	2	3	4	5	6	7	8	9	10	1′	2′,6′	3′,5′	4′
II	−17,8	+31,71	−5,04	−0,65	−0,4	+0,15	+0,44	−1,41	−2,42	−0,21	+1,63	−0.34	−1,48
III	−15,97	+33,56	−10,89	−0,45	+0,08	+0,52	+0,49	−1,26	−0,16	−1,04	+2,24	−0,17	−0,47
IV	+1,26	−1,55	+5,32	+30,63	−13,81	+2,58	−10,26	+3,93	−13,47	−0,86	+0,69	+0,47	+0,11
V	−2,99	+1,09	−1,61	+33,71	−14,94	+0,71	−10,64	+1,56	−9,87	−0,65	0,0	+0,20	+0,14

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*$\Delta\delta = \delta^{13}C(II\text{-}V) - \delta^{13}C(I)$.

TABLE 3. Values of the Electron Densities (qπ) of Compounds (I)-(V)

Compound	Number of the carbon atom												
	2	3	4	5	6	7	8	9	10	1′	2′, 6′	3′, 5′	4′
I	0,011	−0,057	0,136	0,029	−0,021	0,016	−0,049	0,014	−0,043	−0,011	−0,001	0,002	0,006
II, III	−0,065	−0,034	0,136	0,029	−0,024	0,017	−0,051	0,019	−0,019	−0,002	−0,009	0,003	−0,002
IV, V	0,012	−0,059	0,142	0,053	−0,074	0,026	−0,079	0,023	−0,093	−0,011	0,003	0,002	0,005

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*The calculation was performed by SCF MO LCAO method [11] by Yu. M. Sapozhnikov of the Irkutsk Institute of Organic Chemistry.

The effects shown by the substituents at C-3 and C-5 on the chemical shift of the carbon atoms of the flavone skeleton can be expressed in terms of the values of $\Delta\delta$ found as the differences between the chemical shifts in unsubstituted flavone (I) and in the corresponding derivatives (Table 2).

A comparison has been made of the values of $\Delta\delta$ obtained for (II-V) and the changes in the π-charge on the corresponding carbon atoms (Δq_π) calculated from the values of q_π (Table 3).

The parameters of the correlation equation $\Delta\delta = a + b\Delta q\pi$ are given below (r is the correlation coefficient, and s is the mean square deviation):

Equation	Compound	*a*	*b*	*r*	*s*
1	I→II	−1,25	334,95	0,877	2,60
2	I→III	−0,29	310,45	0,894	2,31
3	I→IV	−1,96	66,02	0,240	6,75
4	I→V	−3,28	91,87	0,408	5,49

Equations (1) and (2) were obtained with the exclusion of the values for C_3, since the ^{13}C chemical shift of this carbon atom, to which a substituent is directly attached, is determined by combination of the effects of the latter (in the first place, the induction effect), and the method of calculating charges takes into account only the redistribution of the π-electron density. Since these factors also play a role for the other atoms of the skeleton, but to a smaller degree, it may be considered that a semiquantitative relationship exists between the experimental and calculated parameters. A different pattern is observed for the 5-substituted flavones (equations 3 and 4), where there is no correlation. As follows from the material given below, a good qualitative connection exists between the chemical shifts in the ^{13}C NMR spectra and the reactivities of the flavones studied. Apparently, the use of the π approximation incorrectly reflects the charge distribution in the 5-substituted compounds.

Let us consider the interconnection of the experimental results obtained from the ^{13}C NMR spectra with the pK values of the hydroxy groups of the flavone derivative.

Methoxy groups at C-3 (III) or C-5 (V) have little effect on the distribution of the charge density in ring B (Table 2). Exceptions are C-2',6' in the first case. The replacement of the 5-OCH_3 group by a hydroxy group (IV) somewhat decreases the electron density in ring B. In actual fact, the acidity of the 4'-hydroxy group in 4',5-dihydroxyflavone (pK_1 = 8.74 [2]) is higher than in 4'-hydroxyflavone (pK = 9.14 [1]). Conversely, a hydroxy group at C-3 raises the electron density on C-4'. The acidity of the 4'-hydroxy group in 3,4'-dihydroxyflavone (pK_1 = 9.2 [1]) falls somewhat in comparison with 4'-hydroxyflavone.

The appearance of nucleophilic substituents at C-5 (IV, V) has a substanial effect on the charge density distribution in ring A. The electron density falls in the meta positions (C-7 and C-9) and rises in the ortho and para positions (C-6, C-8, C-10). It may be assumed that the acidities of 6- and 8-hydroxy groups introduced additionally into 5-hydroxyflavone should be lower, and that of a 7-hydroxy group higher, than when these groups are introduced into the flavone molecule (I). This is in good agreement with the fact that in 5,7-dihydroxyflavone pK_1 = 7.4 [12], while in 7-hydroxyflavone pK = 8.12 [1].

Nucleophilic substituents at C-3 (II and III) also show a substantial influence on the distribution of the electron density in ring A as compared with flavone. Under the influence of an OCH_3 group the electron density falls in the C-6, C-7, and C-8 positions and rises at C-5, C-9, and C-10. The electron density in ring A of 3-hydroxyflavone is higher than in 3-methoxyflavone and unsubstituted flavone. An exception is formed by C-7 and C-8, where it varies only slightly, which agrees well with the fact that the 7-hydroxy groups in 3,7-dihydroxyflavone (pK_1 = 8.3 [1]) and in 7-hydroxyflavone have similar ionization capacities.

In contrast to the 5-substituted flavones, where substituents exert a direct influence on the chemical shift of the carbon atoms in ring A and, consequently, on the electron density distribution in it, the case of the 3-substituted flavones this influence is transformed through the state of the carbonyl group and the ether oxygen of the pyrone ring. As can be seen from Tables 1 and 2, the introduction of nucleophilic substituents at C-3 leads to changes in the chemical shifts of the pyrone fragment that are analogous in direction to those observed on the introduction of the same substituents into an aromatic system (benzene) [13]: the signals of the carbon atoms in the ortho and para positions shift upfield, and the signal of the carbon atom to which the substituent is attached shifts downfield.

On this basis, it may be concluded that a nucleophilic substituent at C-3 leads to an increase in the aromaticity of the pyrone fragment and to a possible stabilization of the pyrylium structure. This conclusion is in harmony with those which we made on the basis of spectral information [5].

It is known [14] that substituents increasing the electron density on the carbonyl carbon lower its reactivity with respect to nucleophilic attack. However, since the C=O bond is readily polarized, part of the excess electron density on the carbonyl carbon is transferred to the oxygen, a result of which is an increased reactivity of the carbonyl oxygen in relation to electrophilic attack, for example, by the proton of an acid. The opposite pattern is observed when the nature of the substituent is reversed. It follows from this that an increase in the electron density at C-4 must lead to a rise in the basicity of the flavones.

The values of $\Delta\delta$ (see Table 2) permit the assumption that for the 3-OR-substituted flavones and 5-methoxyflavone there is an increase in the electron density at C-4, and for 5-hydroxyflavone a decrease due to the formation of an intramolecular hydrogen bond. Consequently, in the series of flavones studied, 5-hydroxyflavone should have a lower basicity than unsubstituted flavone, and 5-methoxy-3,5-methoxy-, 3-hydroxy-, and 3-methoxyflavones higher basicities. In actual fact, the basicity of 5-methoxyflavone is higher ($pK_{base} = -1.22$ [5]) and that of 5-hydroxyflavone is lower ($pK_{base} = -3.07$ [3]) than for unsubstituted flavone ($pK_{base} = -1.33$ [3]).

Contrary to expectations, the basicities of 3-substituted flavones [3] are lower than that of unsubstituted flavone. In our opinion, this anomoly is due to the steric influence of the substituent at C-3 on the screening of the closest carbon atoms in the ^{13}C NMR spectrum and does not reflect on direct change in the charge on the atom. At the same time, it may be that it is not magnitude of the charge but steric factors that exert a substantial influence on the basicities of the 3-substituted flavones. A still greater reduction in basicity is characteristic for 3-amino- and 3-bromoflavones [15].

Thus, by means of spectral characteristics it has been strikingly confirmed that the causes of the lowering of the basicities of 3- and 5-hydroxyflavones are different. The interconnection of the chemical shifts of the ^{13}C nuclei in the 3- and 5-substituted flavones with their chemical properties evaluated in terms of the acidity and basicity constants that has found in the present work shows the possibility of using these spectral characteristics for predicting the reactivities of flavones. A quantitative estimate may become possible when the mass of experimental results is broadened.

EXPERIMENTAL

The ^{13}C NMR spectra were recorded on a Varian CFT-20 spectrometer working in the Fourier regime. The compounds were studied in the form of solutions in $(CD_3)_2SO$ having a concentration of 25 mg/ml with the addition of 5 vol.% of TMS, placed in tubes with an internal diameter of 5 mm at 30°C. Under monoresonance conditions about 20,000 Fourier responses were summed, and under the conditions of double $^{13}C-\{^1H\}$ resonance 1,000 responses. The chemical shifts were calculated relative to TMS and their reproducibilities were determined experimentally (±0.02 ppm for a reproducibility of the concentration of ±1% and the same conditions of recording the spectra).

The precedures for synthesizing the flavones (II-V) and their chemical characteristics have been given in previous papers [1-3].

SUMMARY

The ^{13}C NMR of a number of 3- and 5-hydroxyflavones and of 3- and 5-methoxyflavones have been studied for the first time and all the signals have been assigned. A comparison of the chemical shifts of the ^{13}C nuclei with the acidity and basicity parameters of the compounds investigated and with the results of calculations of π-charge density has been made. It has been shown that the chemical shifts of the individual signals in the ^{13}C NMR spectra are qualitatively connected with estimates of the reactivities of the compounds studied.

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STRUCTURES OF ANGRENDIOL, FEROLIN, AND CHIMGANIDIN

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We have previously reported the isolation from the roots of Ferula pallida Eug. Kor. and Ferula tschimganica Lipsky of two new esters, which were called ferolin (I) and chimganidin (II) [1, 2]. On saponification, both substances were cleaved, forming a sesquiterpene diol with the composition $C_{15}H_{26}O_2$, identical with angrendiol (III) described previously [3] and one mole of an acid – p-hydroxybenzoic acid (IV) from (I) and vanillic acid (V) from (II). Consequently, ferolin and chimganidin are monoesters of the acids mentioned and of the same diol. N. P. Kir'yalov has previously isolated angrendiol in the free state from the resins of a number of species of Ferula and has shown that it has a bicyclic carbon skeleton with one double bond and two secondary hydroxy groups [3], but the question of its structure has remained open.

In the present paper we give the results of a determination of the structure of the diol itself and of the positions of the acid residues in the substances that we have isolated. The UV spectrum of (III) has a maximum at 210 nm (3.18), which is characteristic for nonconjugated dienic compounds [4], and its IR spectrum has adsorption bands at 3430 cm^{-1} (hydroxy group) and 1660 cm^{-1} and its IR spectrum has adsorption bands at 3430 cm^{-1} (hydroxy group) and 1660 cm^{-1} (double bond).

In the PMR spectrum of angrendiol (III) (Fig. 1), a six-proton singlet with its center at 1.01 ppm, consisting of two doublets, is due to the methyl of an isopropyl group. Two three-proton singlets at 1.58 and 1.37 ppm are due to methyl groups at a double bond and a hydroxy group, respectively. A proton geminal to a hydroxy group appears in the spectrum in the form of a quartet at 4.16 ppm with $^3J = 11.4$ and 5.3 Hz.

When (III) was acetylated with acetic anhydride in pyridine, a diacetyl derivative was obtained with the composition $C_{19}H_{30}O_4$ (VI) the IR spectrum of which lacked the absorption band of hydroxy groups, while in the PMR spectrum, in addition to the disappearance of the two-proton broadened singlet at 3.10 ppm due to two hydroxy groups, a paramagnetic shift of the signals of the proton in the geminal position to a hydroxy group ($\Delta\delta = 1.20$ ppm) and of the tertiary methyl group at the other hydroxyl ($\Delta\delta \simeq 0.1$ ppm) was observed.

These results show that in actual fact one of the hydroxy groups is secondary and the other is tertiary, being present in the geminal position to a methyl group.

As can be seen from Fig. 1, in the region of olefinic protons there are three doublet signals at 4.62, 4.89, and 5.11 ppm, the lines of which are appreciably broadened. These signals are not present in the spectrum of the tetrahydroderivative (VII), with the composition $C_{19}H_{34}O_4$, obtained by the hydrogenation of angrendiol diacetate over platinum in acetic acid, i.e., (III) has not one but two double bonds.

The presence of an isopropyl group and two methyl groups and of two double bonds shows that, with the composition $C_{15}H_{26}O_2$, angrendiol probably has the monocyclic structure of germacrane.

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