Chemistry of Heterocyclic Compounds, Vol. 30, No. 2, 1994

STUDY OF PMR SPECTRA AND STRUCTURE OF HETEROCYCLIC ANALOGS OF CHALCONE

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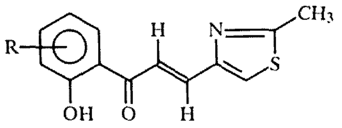
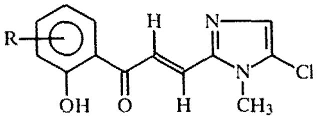
A study was made of the PMR spectra of heterocyclic analogs of chalcone containing thiazole, imidazole, benzofuran, and pyridine residues. The shift patterns were determined of the signals under the influence of an aromatic solvent. Through experiments made on the Overhauser homonuclear effect the signals were reliably assigned and the orientation of the heterocyclic fragments in the molecules of chalcones was established.

The heterocyclic analogs of chalcone are important intermediates for the synthesis of 2- and 3-hetarylchromones, which exhibit a broad spectrum of biological activity. Several reports have been published on the structure, the spectral and conformational features of these compounds [1, 2], but there still remains some ambiguity with respect to the assignment of signals for the olefinic protons in the PMR spectra of chalcones with various heterocyclic rings, and, moreover, the orientation with respect to the vinyl protons has not been established for most of the heterocyclic substituents.

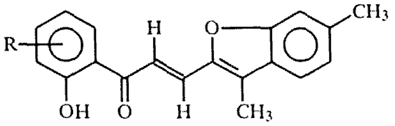
We have previously shown [3] that in the case of benzodioxane and benzodioxepane derivatives of chalcones, the conformational features of the products can be clarified by evaluating the shifts induced by an aromatic solvent (SIAS). We therefore also tried to use this method for other heterocyclic analogs containing the thiazole, imidazole, benzofuran, and pyridine fragments:



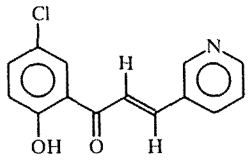
I-III



IV-VI



VII, VIII



IX

The synthesis of compounds I-IX has previously been described in [4-6]. The values of the chemical shifts found are given in Table 1. It is seen that for the signals of the individual protons of the compounds studied there are considerable shifts into the weak or strong magnetic field under the influence of benzene. The strongest paramagnetic shift occurs in the signal of the hydroxyl proton (up to 0.9 ppm). Shifts of similar extent, and in several cases still larger diamagnetic ones are observed for the signals of protons bound to the heterocyclic fragment. The shift into the strong field of the signal of the N-methyl group of the imidazole derivatives IV-VI by the action of benzene is particularly remarkable. Here the effect reaches 1.4 ppm, which in its absolute values exceeds the shifts occurring during the protonation of the imidazole ring.

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0009-3122/94/3002-0222$12.50

TABLE 1. PMR Spectral Data of the Heterocyclic Analogs of Chalcone, δ, ppm

Compound	Heterocyclic ring R	Solvent	The phenol part protons					Olefinic protons		Heterocyclic ring protons					
			2-OH	3-H	4-R	5-R	6-H	α-H	β-H	1-R	2-R	3-R	4-H	5-H	6-H
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
I	2-Methyl-4-thiazolyl	$CDCl_3$	12,67	6,92	H; 7,31	CH_3; 2,35	7,79	7,97	7,70	—*	CH_3; 2,80	—	—	7,43	—
		C_6D_6	13,44	6,98	H; 6,84	CH_3; 1,82	7,53	8,25	7,79	—	CH_3; 2,18	—	—	6,51	—
		SIAS	0,77	0,06	-0,47	-0,53	-0,26	0,28	0,09	—	-0,62	—	—	-0,92	—
II		$CDCl_3$	12,89	6,82	CH_3; 2,36	H; 6,73	7,89	7,96	7,72	—	CH_3; 2,77	—	—	7,39	—
		C_6D_6	13,64	6,83	CH_3; 1,89	H; 6,32	7,53	8,19	7,74	—	CH_3; 2,18	—	—	6,46	—
		SIAS	0,75	0,01	-0,47	-0,40	-0,36	0,25	0,02	—	-0,59	—	—	-0,93	—
III		$CDCl_3$	12,44	6,95	H; 7,14	OCH_3; 3,84	7,43	7,94	7,77	—	CH_3; 2,77	—	—	7,42	—
		C_6D_6	13,23	6,97	H; 6,82	OCH_3; 3,12	7,27	8,18	7,79	—	CH_3; 2,15	—	—	6,48	—
		SIAS	0,75	0,02	-0,32	-0,72	-0,16	0,24	0,02	—	-0,62	—	—	-0,94	—
IV	1-Methyl-5-chloro-2-imidazolyl	$CDCl_3$	12,72	7,00	H; 7,50	H; 6,92	7,97	8,09	7,66	CH_3; 3,74	—	—	7,15	—	—
		C_6D_6	13,45	—	H; 7,01	—	7,54	8,22	7,39	CH_3; 2,36	—	—	7,00	—	—
		SIAS	0,73	—	-0,49	—	-0,43	0,13	-0,27	-1,38	—	—	-0,15	—	—
V		$CDCl_3$	12,40	6,95	H; 6,15	OCH_3; 3,83	7,39	8,05	7,69	CH_3; 3,75	—	—	7,18	—	—
		C_6D_6	13,18	6,98	H; 6,96	OCH_3; 3,21	7,35	8,31	7,44	CH_3; 2,35	—	—	6,96	—	—
		СИАР	0.78	0.03	-0.21	-0.62	-0.04	0.26	-0.25	-1.40	—	—	-0,24	—	—

TABLE 1. (continued)

Compound	Heterocyclic ring R	Solvent	The phenol part protons					Olefinic protons		Heterocyclic ring protons					
			2-OH	3-H	4-R	5-R	6-H	α-H	β-H	1-R	2-R	3-R	4-H	5-H	6-H
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
VI		$CDCl_3$	13,34	6,42	OCH_3; 3,85	H; 6,48	7,87	7,97	7,63	CH_3; 3,72	—	—	7,13	—	—
		C_6D_6	14,21	6,46	OCH_3; 3,12	H; 6,23	7,50	8,23	7,47	CH_3; 2,42	—	—	7,03	—	—
		СИАР	0,87	0,04	-0,73	-0,25	-0,37	0,26	-0,16	-1,30	—	—	-0,1	—	—
VII	3,6-Dimethyl-6-benzofuryl	$CDCl_3$	12,65	6,96	H; 7,09	OCH_3; 3,87	—	7,60	7,89	—	—	CH_3; 2,40	—	—	CH_3; 2,49
		C_6D_6	13,25	6,99	H; 6,83	OCH_3; 3,23	7,27	7,69	7,97	—	—	CH_3; 1,82	—	—	CH_3; 2,13
		СИАР	0,60	0,03	-0,26	-0,64	—	0,09	0,08	—	—	-0,58	—	—	-0,36
VIII		$CDCl_3$	12,76	6,92	H; 7,32	CH_3; 2,37	7,77	7,66	7,90	—	—	CH_3; 2,50	—	—	CH_3; 2,41
		C_6D_6	13,51	7,02	H; 6,87	CH_3; 1,91	7,52	7,79	8,02	—	—	CH_3; 1,81	—	—	CH_3; 2,14
		СИАР	0,75	0,1	-0,49	-0,46	-0,25	0,13	0,12	—	—	-0,69	—	—	-0,27
IX	3-Pyridyl	$CDCl_3$	12,53	7,00	H; 7,44	Cl	7,85	7,61	7,94	—	H; 8,89	—	8,00	7,44	H; 8,69
		C_6D_6	13,07	6,73	H; 6,93	Cl	7,48	6,55	7,83	—	H; 8,48	—	6,96	6,59	H; 8,41
		СИАР	0,54	-0,27	-0,51	—	-0,37	-0,06	-0,11	—	-0,41	—	-1,04	-0,85	-0,28

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*Magnetic nuclei are absent in the corresponding substituent; the absence of a numeral means that an accurate value of the chemical shift could not be found because of the overlapping of signals. The SSCC values were published in [4-6].

For the signals of the olefinic protons the SIAS values are relatively small. They, as the chemical shifts themselves, are dependent on the type of the heterocyclic fragment and the presence of substituents in the molecule. It is important here that unlike for the previously studied benzodioxane and benzodioxepane derivatives [3], it is impossible on the basis of the SIAs to assign the signals, and hence to determine the conformation of the molecules. This is probably due to the fact that the electron acceptor heterocyclic rings in the molecules of I-IX are coordinated with the molecule of benzene much more effectively than the carbonyl group. The SIAS values of the olefinic protons are thus determined mainly by the coordination of the heterocyclic fragment and not of the carbonyl group with benzene. Thus, the Connoly and McGrindle model [7] is in this case inapplicable for the determination of the conformationally mobile fragments bound to the carbonyl group.

For a reliable assignment of signals of the olefinic protons in the compounds studied we used the Overhauser homonuclear effect. The additional irradiation at the frequency of protons bound to the aromatic rings located at different sides of the olefinic fragment makes possible the reliable assignment of signals of the latter, which is facilitated by the relative simplicity of the PMR spectra and the possibility of selective irradiation at the frequencies of signals of the majority of the protons of the molecules studied. In the thiazole derivatives, the irradiation at the frequency of the 5-H proton of the thiazole ring causes an increase in the intensity of the strong-field signal of one of the olefinic protons ($n_{\beta-H}$ {5H} = 5%), indicating that this signal in particular belongs to the β-H proton (relative to the carbonyl group). A similar experiment with the imidazole derivatives IV-VI with the irradiation at the frequency of the $N-CH_3$ group signal led to an increase in the intensity of the signal of the strong-field olefinic proton by 12% on the average. Thus, also in these compounds the β-H proton absorbs in the stronger field. These results do not conform with the conclusions made earlier for chalcone containing electron-donor heterocyclic rings of benzodioxane and benzodioxepane, in which the assignments of signals are confirmed by analysis of the spectra of α-deuterium-containing chalcones [3]. In benzofuran derivatives VII, VIII, upon irradiation at the frequency of the $3\text{-}CH_3$ group signal of the benzofuran fragment, the intensity of the weak-field olefinic signal increases ($n_{\beta-H}$ {$3\text{-}CH_3$} = 8%). On the other hand, in the experiment with the irradiation at the frequency of the 6-H benzene ring signal, the intensity of the strong-field signal of the olefinic protons noticeably increases ($n_{\beta-H}$ {6-H} = 6%), wherefrom it follows that in the benzofuran derivatives the signal of the β-H olefinic proton absorbs in the weaker field. The same result was also obtained for the 3-pyridyl-containing chalcone IX. In this case, because of the presence of a large number of signals, the Overhauser nuclear effect (ONE) experiments were carried out in the presence of a lanthanoid shifting reagent (LSR)-$Eu(FOD)_3$. Under these conditions, a first order spectrum was obtained for the product showing a large separation between the peaks. On additional irradiation at the frequency of the weak field signal of the olefinic protons (β-H), the intensity of the 4-H pyridine proton increases very strongly (by 28%). In an experiment with the suppression at the frequency of the 6-H proton of the benzene ring, the intensity of the signal of the α-H olefinic proton increases by 19%, and at the irradiation at the frequency of the 2-H pyridine proton — by 8%.

In the pyridine-containing product IX, according to the ONE data, an alternative planar orientation of the pyridine ring was not detected, as indicated by the absence of a noticeable ONE of the 2-H pyridine proton at {β-H}, clearly due to the fact that the measurements were not carried out with a pure preparation, but with its adduct with the LSR, for which, because of coordination with the paramagnetic lanthanoid ion, the relaxation time of the 2-H proton is considerably reduced, and as a result the ONE value of this signal decreases.

The ONE experiments also make it possible to find the conformation of the chalcones. It was found to be as depicted in the structural formulas of I-IX. Since the values of the homonuclear ONE are usually proportional to $1/r^6$ (r is the distance between the interacting protons), the presence of ONE clearly indicates a steric proximity of the protons between which the effect is observed, and hence the conformation of the molecule is correspondingly fixed.

EXPERIMENTAL

The PMR spectra of products I-IX were measured on a Bruker WP-100 SY spectrometer with a working frequency of 100.13 MHz. The chemical shifts were found relative to TMS (internal standard). The ONE experiments were carried out by standard methods. A commercially available $Eu(FOD)_3$ was used as the LSR.

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