Syntheses and NMR Spectroscopic Studies on the Conformations of 1-[1-(2-Aralkyloxy- and 2-Acyloxyphenyl)vinyl]-1*H*-Imidazoles[1)]

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Synopsis. The title compounds were synthesized from 2-[1-(1-imidazolyl)vinyl]phenol and their conformations were discussed on the basis of their ^{1}H and ^{13}C NMR spectra.

In recent decades, antifungal substaces have attracted considerable interests from pharmaceutical and agricultural points of view, and many investigations concerning their syntheses, structural elucidations, and biological activities have been reported.[2-4)] The present authors have also been studying a series of antifungal imidazole derivatives.[5,6)] One of our recent research includes the syntheses, NMR spectra, and antifungal activities of 4-(substituted aryl)-2-(1-imidazolyl, 1-pyrazolyl, and 1,2,4-triazol-1-yl)-1,3-dioxolanes.[7,8)]

In this connection, we synthesized several heterocyclic analogs of the above imidazole derivative and acyl derivatives of 2-[1-(1-imidazolyl)vinyl]phenol (**19**).[4)] Their syntheses, NMR spectroscopic studies, and antifungal activities are reported in this paper.

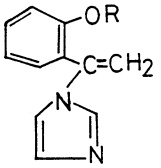
Experimental

The (imidazolylvinyl)phenol **19** was obtained by the reaction of *o*-hydroxyacetophenone and *N*,*N*′-sulfinyldiimidazole, prepared by adding thionyl chloride to a suspension of imidazole in dichloromethane.[4)] Then, acyl chloride (0.0176 mol) was added gradually to an ice-cooled pyridine solution (30 ml) of the phenol **19** (0.016 mol). The reaction mixture was kept standing for additional 10 min. The whole was poured into water and extracted with dichloromethane. Thus obtained crude products **1**—**14** were recrystallized or distilled in vacuo, and purified further by column chromatography on silica gel. Similarly ethers **15**—**18** were prepared by treating potassium phenolate of **19** with the corresponding arylmethyl chlorides in *N*,*N*-dimethylformamide.

^{1}H and ^{13}C NMR spectra were recorded on a JEOL FX-90Q spectrometer.

Results and Discussion

Various 1-[1-(2-aralkyloxy- and 2-acyloxyphenyl)-vinyl]-1*H*-imidazoles **1**—**18** were prepared starting form known 2-[1-(1-imidazolyl)vinyl]phenol (**19**). Most of them were prepared newly by the present authors and characterized by their physical properties, NMR spectra, and elemental analyses.



1; R=CH_3CO **2**; R=C_2H_5CO
3; R=C_3H_7CO **4**; R=C_4H_9CO
5; R=$C_5H_{11}CO$ **6**; R=4-FC_6H_4CO
7; R=4-ClC_6H_4CO **8**; R=4-BrC_6H_4CO
9; R=4-$CH_3C_6H_4CO$ **10**; R=4-$CH_3OC_6H_4CO$
11; R=3-ClC_6H_4CO **12**; R=3-BrC_6H_4CO
13; R=3-$CH_3C_6H_4CO$ **14**; R=2,4-$Cl_2C_6H_3CO$
15; R=4-Pyridylmethyl **16**; R=2-Pyridylmethyl
17; R=2-Thienylmethyl **18**; R=5-Cl-2-thienylmethyl
19; R=H

These *N*-(1-arylvinyl)imidazoles are structurally similar to cloconazole[4)] and potential antibacterial and antifungal agents.[7,8)] Since the biological activity is closely related with the shape of the active molecule, the conformations of the *N*-(1-arylvinyl)imidazoles **1**—**19** were elucidated by ^{1}H and ^{13}C NMR spectroscopy. The ^{13}C NMR chemical shifts are given in Table 1.

As the shapes of the *N*-(1-vinylaryl)imidazole molecules are expected to be altered most significantly by the conformational change caused by the rotations about the C-C bond connecting vinyl and *o*-R-oxyaryl groups, the C-N bond connecting vinyl and imidazolyl groups, and the C-O bond connecting the aryl and R-oxy groups, the substituent effect on the spectra of vinylidene groups were examined most carefully. Overviewing Tables 1 and 2, chemical shifts of vinyli-

Table 1. ^{13}C NMR Chemical Shifts

Compd	Vinylidene		Aromatic						Imidazolyl			CO/CH_2
	C_{alpha}	C_{beta}	1	2	3	4	5	6	2′	4′	5′	
1	139.3	107.2	128.6	148.2	123.3	130.6	126.6	130.6	118.2	129.6	136.2	168.5
2	139.4	107.2	128.7	148.4	123.3	130.8	126.2	130.8	118.2	129.7	136.2	172.1
7	139.2	107.4	128.4	148.4	123.4	131.0	126.7	131.0	118.3	129.7	136.2	163.6
9	139.3	107.4	128.9	148.9	123.7	130.9	126.4	130.9	118.3	129.7	136.3	164.6
14	138.2	106.7	128.1	147.4	122.2	130.2	126.0	130.3	117.4	128.7	135.3	161.2
15	140.7	105.9	121.5	155.5	112.1	131.2	124.9	131.4	117.8	129.3	135.9	68.2
16	140.9	105.9	121.2	156.3	112.5	131.3	125.0	131.4	117.8	129.6	136.2	70.9
17	140.4	106.6	121.4	156.0	113.0	130.9	125.5	131.2	117.9	129.3	136.2	65.5
18	140.2	106.6	121.6	155.6	112.8	130.5	125.3	131.2	117.9	131.0	137.2	65.4

dene carbons (C_α and C_β), as well as those of protons (H_a and H_b), were rather insensitive to the modifications in the acyl side chain.

The vinylidene ^{13}C chemical shifts were dependent on whether the side chain is acyloxyl or aralkyloxyl. The effect might be induced by a through-bond perturbation since the α-carbon connected directly to the aromatic carbon ortho to the RO group is affected more significantly. The through-bond effect of the RO group should be transmitted in an alternate manner causing high and low field shifts alternately and decaying gradually due to the pi-electron releasing mesomeric effect by RO group.[9,10] The observed ^{13}C chemical shifts are in accord with the above reasoning and can be rationalized if we assume that the original perturbation by an aralkyloxyl group is larger than that by an acyloxyl group.[11]

The vinylidene proton signals appeared as AX quartets. The signals at lower fields are assigned to the proton cis to the aryl group (hereafter designated as H_a) and the one at the higher fields to the proton cis to the imidazolyl group (hereafter designate as H_b) (Table 2). Geminal coupling constants J_{ab} are small, ranging from 1.0 to 1.2 Hz, and insensitive to the substituent and solvent effects. Modification of the side chain from aliphatic acyl group to aroyl causes a small but discernible high field shift of H_a signal in chloroform solutions. The shift might be ascribed to the anisotropy effect due to the aroyl aromatic ring. However the effect is obscured in other solvents.

As revealed by the chemical shifts of H_a and H_b in various solvents (in Table 2), their chemical shifts are susceptible to the solvent effect. Especially H_a is very sensitive to the nature of solvents and shows general tendency to shift considerably towards upfield in benzene-d_6 and, in contrast, to shift towards downfields in pyridine-d_5 and DMSO-d_6. With a very minor exception which shows the reversal of the order within an experimental error, the H_a signals are subjected to the solvent effect which aligns the chemical shifts in the order (from the high field); benzene>chloroform>pyridine>dimethyl sulfoxide. The upfield shifts in benzene is rather larger than the usual aromatic solvent induced shifts (ASIS) expected for this sort of proton. The larger shift might be caused by the acidic character of H_a, since ASIS is supposed to be originated from weak C-H···pi hydrogen bonding,[13] The acidity seems plausible if we consider the fact that the vinylidene protons occupy the positions vinylogous to acidic imidazole NH. As a large ASIS was not observed with the beta-protons of *o*-methoxy styrene (**20**), the importance of acidity in ASIS becomes more evident. Benzene induced shifts including the protons and carbons of other parts of the molecule were also examined with several of the *N*-(1-arylvinyl)imidazoles. Generally speaking, positively charged hydogen (and carbon) atoms orienting themselves toward outside the molecule showed the positive ASIS in accord with the reported trend of ASIS[12] and theoretical consequences. Besides those given in Table 2, the ^1H ASIS of arylmethoxyl CH_2 groups of **15—18** comes to be +0.75, +0.23, +0.55, and 0.57,

Table 2. Chemical Shifts of Vinylidene Protons H_a and H_b and T_1 Values in $CDCl_3$

Compd	^1H-Chemical shift δ/ppm (from TMS)								T_1/s		
	In $CDCl_3$		In C_6D_6		In C_5D_5N		In $(CD_3)_2SO$				
	H_a	H_b	H_a	H_b	H_a	H_b	H_a	H_b	H_a	H_b	CH_2
1	5.43	5.15	4.89	4.68	5.50	5.10	5.63	5.12	0.55	0.87	
2	5.43	5.10	4.84	4.64	5.51	5.09	5.63	5.11			
4	5.43	5.10	4.84	4.64	5.53	5.09	5.57	5.10	0.53	0.83	
7	5.38	5.07	4.82	4.68	5.46	5.11	5.56	5.14	0.60	0.76	
9	5.35	5.13	4.84	4.77	5.46	5.13	5.61	5.15	0.60	0.76	
14	5.44	5.15	4.85	4.67	5.55	5.14	5.68	5.18			
15	5.44	5.11	4.93	4.22	5.55	5.08	5.63	5.10	0.34	0.68	0.83
16	5.45	5.12	4.94	4.69	5.54	5.09	5.59	5.05	0.93	1.09	1.11
17	5.40	5.13	4.92	4.74	—	—	5.59	5.04	1.13	1.30	1.30
18	5.41	5.11	4.95	4.74	5.51	5.06	5.61	5.03	0.97	1.02	1.03
19	5.43	5.14	4.83	4.71	5.57	5.25	5.55	5.08	0.50	0.53	
20	5.73	5.24	5.74	5.20	5.83	5.27	5.79	5.25	2.79	2.70	

Table 3. Antibacterial and Antifungal Activities (MIC, mg l^{-1})

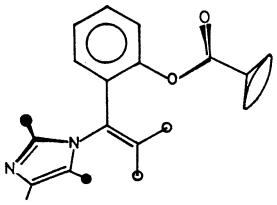
Organism	Compound						
	1,2,5,7,9,14	**3,8**	**4**	**15**	**16**	**17**	**18**
Staphylococcus aureus FDA209P	*	*	*	50	50	*	100
Escherichia coli NIHJ	*	*	*	*	*	*	*
Candida albicans YU-1200	*	*	*	50	50	25	3.12
Aspergillus melleus IFO4339	*	100	50	50	50	50	50
Aspergillus orizeae	*	*	*	50	50	12.5	12.5
Trychophyton mentagrophytes IFO833	*	*	*	12.5	25	3.12	12.5
Trychophyton asteroides 429	*	*	*	12.5	25	1.56	3.12
Penicillium chrisogenum ATCC10002	*	*	*	25	50	1.56	1.56

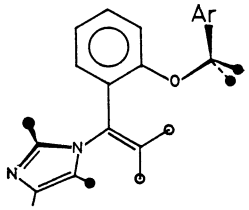
respectively, and that of the terminal methyl group of acyloxyl side chain in the series of compounds **1**—**5** is shown to decrease as the alkyl chain of the acyl group elongates (i. e., +0.39 for **1**, +0.20 for **2**, +0.17 for **3**, +0.13 for **4**, and +0.08 for **5**). As expected, relatively positive ^1H ASIS were observed with the CH_2 groups bonded to oxygen and the CH_3 in acetyl group of **1** which are expected to be considerably acidic owing to the inductive effect of adjacent electronegative groups.

In order to estimate the preferred conformation about the C_{vinyl}-C_{aryl} and C_{vinyl}-$N_{imidazoyl}$ bonds qualitatively, several NOE experiments were carried out. The irradiation of hetarylmethoxyl CH_2 protons in **15**—**17** enhanced the intensities of H_a in 4—10% (**15**, 5%; **16**, 4%; **17**, 10%; and **18**, 10%) in reference to other unirradiated protons. Similarly the irradiation of acetoxyl CH_3 protons in **1** caused the 3% enhancement of H_a signal. As the enhancement was rather small, the increase in intensity was ascertained by several repetitions of the measurements. The NOE experiments showed unambiguously that the acyloxyl or arylmethoxyl group is located syn to the vinylidene group with respect to the C_{vinyl}-C_{aryl} bond, taking a nearly coplanar conformation judging from the observed enhancement. In contrast, the imidazolyl ring should be nearly perpendicular to the plane of vinylidene moiety, keeping the 2′- and 5′-hydrogens farther than 3.4 Å away from both H_b and H_a of vinylidene moiety, since no enhancement of the H_a signal was observed by the irradiation of 2′-H and 5′-H. If we assume that the carbonyl group is exactly coplanar to the aryloxyl moiety, methyl group in **1** is located too far from H_a to observe NOE enhancement. However, the carbonyl group is expected to be twisted to a certain extent around $C_{carbonyl}$-$O_{aryoxyl}$ bond and pushed away from the aryloxyl plane in order to reduce the steric hindrance by 3-hydrogen atom on the benzene ring. In this conformation, methyl group should approach nearer to H_a, which enables us to observe the small enhancement. Judging from their chemical shifts of H_a higher than those of **1**—**5**, similar conformations in which H_a approaches from above the plane of aroyl aromatic ring might be realized. Analogously the pyridine and thiophene rings are assumed to occupy a position considerably deviated from the plane of vinylidenearyloxyl part of the molecule.

If the vinylidenearyloxyl moiety is nearly coplanar as stated above, one of the vinylidene hydrogen H_a should lie very close (as close as 1.63 Å, if completely coplanar) to the aryloxyl oxygen atom. When an acidic hydrogen is in the proximity of electronegative oxygen atom, C-H ··· O hydrogen bond is expected to be formed. T_1 measurements showed that the H_a has somewhat shorter T_1 than H_b and other hydrogens in the molecule. When the T_1 values were compared with those in *o*-methoxystyrene (**20**), T_1 values of H_a and H_b are generally short. The results imply the fact that the motion of H_a is significantly restricted in these molecules. Intramolecular C-H ··· O hydrogen bond may persist under such sterically favored circumstances, which, in turn, contributes to stabilize the planar vinylidenearyloxyl moiety.

In conclusion, following sketches for the steric structures of the title compound 1-(1-arylvinyl)-imidazoles can be drawn. This is in accord with the X-ray result recently reported by Ogata and coworkers,[14] and the solution structure was shown to be similar to that in crystal.





Antifungal and antibacterial activities of the 1-(1-arylvinyl)imidazoles are given in Table 3. The hetarylmethoxyl derivatives **15**—**18** are shown to have broad spectrum fungicidal and bacteriocidal activities, while the acyloxyl derivatives **1**—**14** are seldom active. The NMR spectroscopic studies showed that the difference in conformations between the hetarylmethoxyl derivatives and the acyloxyl derivatives is very slight in contrast to the remarkable difference in biological activities.

Since the acyloxyl derivatives are rather susceptible to hydrolysis and some of them are sensitive to atmospheric moisture, the instability might be the reason for the discrepancy. However, further investigation is necessary before ascribing the inactivity of the acyloxyl derivative to the hydrolytic degradation.

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