^{13}C-NMR Spectra of 2-Aryl-2-(1-azolylmethyl)-4-hydroxymethyl-1,3-dioxolanes and Their Ester and Ether Derivatives

Hiroko SUEZAWA,* Minoru HIROTA, Kazuko YAMAMOTO,†
Isao TAKEUCHI,† and Yoshiki HAMADA†

Department of Applied Chemistry, Faculty of Engineering, Yokohama National University, Tokiwadai, Hodogaya-ku, Yokohama 240

†Faculty of Pharmacy, Meijo University, Tempakucho, Tempaku-ku, Nagoya 468

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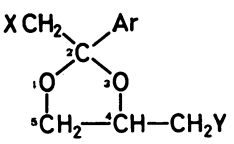
Synopsis. The ^{13}C-NMR spectra of the title compounds were assigned and the substituent effect was discussed briefly. ^{13}C-NMR of 2-aryl-4-benzoyloxymethyl-2-bromomethyl-1,3-dioxolanes provides the way to discriminate the cis and the trans isomers.

4-(Substituted aryl)-2-(1-imidazolyl)-1,3-dioxolanes have been shown to have antifungal activities towards *Microporum canis, Ctenomyces menlagrophytes, Trichophyton rubrum,* and other fungi.[1] These compounds are also active to some gram-negative and gram-positive bacilli. The antifungal and bactericidal activities are known to be sensitive to the stereochemistry of these compounds.

In our recent investigations on a series of the title compounds carrying 1-pyrazolyl, 1-imidazolyl, 1,2,4-triazol-1-yl, and 1-tetrazolyl groups as azolyl group (X in formula I), a number of their derivatives which are analogous to the azolyldioxolanes were synthesized from the corresponding 2-bromomethyl-1,3-dioxolanes.[2] Since the 2- and 4-carbon atoms of the dioxolane ring are asymmetric, two pairs of enantiomers mutually diasteromeric to each other are possible.



Formula I.

The pharmaceutical activities are strongly dependent on the stereochemistry. *r*-2-(1-Azolylmethyl)-2-(2,4-dichlorophenyl)-*c*-4-hydroxymethyl-1,3-dioxolanes and their derivatives are usually far more active than the other diastereomers, *t*-4-hydroxymethyl compounds.[3]

In this paper, ^{13}C-NMR spectral data of these dioxolanes are reported and their possobility to use for assigning the diastereomers.

Experimental

Preparation of the materials was reported elsehwere.[2,4] NMR spectra were recorded on a JEOL JNM FX-90Q spectrometer usually in chloroform-*d* solutions. The assignment of ^{13}C-NMR spectra were carried out by use of off-resonance technique. Aromatic carbon resonances were estimated by the additivity values[5] and by mutual comparison of the spectra. In some cases, selective decoupling technique was also employed.

Results and Discussion

^{13}C-Chemical shifts of 2-(1-azolylmethyl)-2-(2,4-dichlorophenyl)-4-hydroxymethyl-1,3-dioxolanes, their methanesulfonates, benzoates, and some of their ethers are given in Table 1. The dioxolanes are mostly cis isomers, which are pharmaceutically more active than the corresponding trans isomers. ^{13}C-Chemical shifts of the cis and the trans isomers of 2-aryl-2-bromomethyl-4-benzoloxymethyl-1,3-dioxolanes are also

TABLE 1. ^{13}C-NMR OF 2-ARYL-2-AZOLYLMETHYL-1,3-DIOXOLAN-4-YLMETHANOL AND THEIR DERIVATIVES

No.	X	Ar	Y		X(Azole Ring)				Dioxolane Ring					Aryl Group (Ar)						Y (or Z-Ar)						
					2	3	4	5	2	4	5	2-CH_2	4-CH_2	1	2	3	4	5	6	Y(Z)	1	2	3	4	5	6
1	pyrazolyl	2,4-$Cl_2C_6H_3$	OH	cis	----	139.8	105.9	131.2	107.9	76.8	65.9	55.9	61.4	135.6	135.1	129.6	133.0	127.0	131.7	OH ----	----	----	----	----	----	----
2			OSO_2CH_3	cis	----	139.4	106.1	131.3	108.9	73.8	68.2	56.0	66.5	135.9	132.4	129.5	133.1	127.2	131.3	CH_3^* 37.6	----	----	----	----	----	----
3			$OCOC_6H_5$	cis	----	139.3	105.7	131.0	108.4	74.1	66.9	56.0	63.9	135.4	134.5	129.6	133.0	126.8	131.0	CO 165.9	131.0	129.6	128.3	133.2	128.3	129.6
4			$OC_6H_3Cl_2$-2,4	cis	----	139.4	105.9	131.3	108.6	74.3	67.4	56.1	68.8	135.7	134.2	129.7	133.2	127.1	131.3	O ----	152.8	123.9	130.1	126.4	127.6	114.5
5	Imidazolyl	2,4-$Cl_2C_6H_3$	OH	cis	139.8	----	128.2	121.3	107.6	77.1	66.9	51.4	61.9	135.9	134.8	129.7	133.0	127.3	131.4	OH ----	----	----	----	----	----	----
6			OSO_2CH_3	cis	138.7	----	128.6	121.2	108.4	73.9	67.7	51.0	66.4	136.1	134.1	129.4	132.9	127.3	131.4	CH_3^* 37.5	----	----	----	----	----	----
7			$OCOC_6H_5$	cis	138.5	----	128.5	120.9	108.1	74.3	67.1	51.5	63.9	135.9	134.2	129.6	132.9	127.2	131.3	CO 166.1	131.3	129.6	128.5	133.3	128.5	129.6
8			$OC_6H_3Cl_2$-2,4	cis	138.9	----	128.6	121.3	108.4	73.9	67.7	51.0	66.4	136.0	134.4	130.1	133.1	127.3	131.5	O ----	152.7	123.7	129.6	126.5	128.6	114.6
9			$SC_6H_3Cl_2$-2,6	cis	138.5	----	128.5	121.0	108.1	76.2	69.4	51.5	36.6	135.7	134.5	129.4	132.9	127.1	131.2	S ----	131.6	141.4	128.7	130.3	128.7	141.4
10	4-NO_2-Im.	2,4-$Cl_2C_6H_3$	OH	cis	138.7	----	146.5	123.2	106.7	76.8	66.9	51.4	61.0	134.8	134.8	130.1	132.5	127.4	130.8	OH ----	----	----	----	----	----	----
11			OSO_2CH_3	cis	137.7	----	147.6	121.4	107.5	74.1	67.1	51.9	66.2	136.7	135.7	129.5	132.9	127.6	131.7	CH_3^* 37.6	----	----	----	----	----	----
12			$OCOC_6H_5$	cis	137.5	----	147.6	121.1	107.3	74.4	66.9	52.1	63.7	136.5	134.4	129.2	133.1	127.5	131.6	CO 166.1	131.6	129.6	128.6	133.4	128.6	129.6
13	2-Me-5-NO_2 -Imid.	2,4-$Cl_2C_6H_3$	OH	cis	144.8	----	123.8	146.4	107.2	76.7	66.8	50.0	61.0	134.9	134.9	130.2	132.5	127.5	130.7	OH ----	----	----	----	----	----	----
14			OSO_2CH_3	cis	146.2	----	122.1	146.7	108.3	74.2	67.1	50.4	60.1	136.8	135.7	129.6	133.1	127.8	131.8	CH_3^* 37.7	----	----	----	----	----	----
15			$OCOC_6H_5$	cis	146.2	----	121.8	146.4	108.0	74.4	66.9	50.7	63.1	136.6	133.6	129.8	133.1	127.7	131.7	CO 166.0	131.7	129.8	128.6	133.4	128.6	129.8
16	Imidazolyl	4-FC_6H_4	$OCOC_6H_5$	trans	138.6	----	128.4	120.9	108.2	74.2	67.0	54.0	64.1	135.0	127.5 127.9	114.9 115.9	157.5 168.6	114.9 115.9	127.5 127.9	CO 166.0	129,7	129.7	128.4	133.3	128.4	129.7
17		4-ClC_6H_4	$OCOC_6H_5$	trans	138.7	----	128.3	120.9	108.5	76.0	66.9	54.7	62.7	134.9	127.1	128.7	138.7	128.7	127.1	CO 166.0	129.7	129.7	128.3	133.3	128.3	129.7
18		4-BrC_6H_4	$OCOC_6H_5$	trans	138.7	----	128.3	120.9	108.5	76.0	66.9	54.6	62.7	138.6	127.3	131.6	123.3	131.6	127.3	CO 166.0	131.6	129.5	128.3	133.3	128.3	129.5
19		4-$CH_3OC_6H_4$	$OCOC_6H_5$	trans	138.7	----	128.5	120.9	108.8	75.7	67.0	54.9	63.2	132.1	126.9	113.8	159.9	113.8	126.9	CO 166.0	132.1	129.6	128.2	133.1	128.2	129.6
20	Triazolyl (1,2,4)	2,4-$Cl_2C_6H_3$	OH	cis	----	151.4	----	145.1	107.2	76.9	66.4	53.5	61.5	135.9	134.2	129.5	132.9	127.3	131.4	OH ----	----	----	----	----	----	----
21			OSO_2CH_3	cis	----	151.4	----	144.9	108.1	73.8	67.6	53.4	66.3	136.2	133.4	129.5	133.0	127.3	131.5	CH_3^* 37.7	----	----	----	----	----	----
22			$OCOC_6H_5$	cis	----	151.4	----	144.7	107.8	74.3	67.0	53.7	63.8	136.0	133.8	129.5	133.0	127.2	131.4	CO 165.9	131.4	129.6	128.5	133.3	128.5	129.6
23			$OC_6H_3Cl_2$-2,4	cis	----	151.3	----	145.0	107.8	74.4	67.4	53.6	68.8	136.2	133.9	129.6	133.2	127.3	131.5	O ----	152.6	123.9	130.1	126.8	127.8	114.7
24			$SC_6H_3Cl_2$-2,6	cis	----	151.5	----	144.9	107.8	76.2	69.4	53.9	37.0	136.0	134.0	129.5	133.2	127.2	131.4	S ----	131.6	141.5	128.9	130.6	128.9	141.5
25	Tetrazolyl (1,2,3,5)	2,4-$Cl_2C_6H_3$	CH_3	cis	----	----	152.6	----	106.5	78.0	69.9	56.9	25.9	135.5	134.5	129.5	133.1	126.9	130.0	CH_3 9.8	----	----	----	----	----	----
26			CH_3	trans	----	----	152.6	----	106.5	79.1	69.6	57.1	25.5	135.7	134.7	129.6	133.2	127.0	131.1	CH_3 9.5	----	----	----	----	----	----
27			OH	cis	----	----	152.8	----	106.9	77.1	66.6	56.7	61.6	135.1	133.9	129.7	133.2	127.2	131.2	OH ----	----	----	----	----	----	----
28			OSO_2CH_3	cis	----	----	152.9	----	107.9	74.0	67.9	56.8	66.3	136.4	134.4	129.6	133.2	127.3	131.5	CH_3^* 37.6	----	----	----	----	----	----
29			$OCOC_6H_5$	cis	----	----	152.7	----	107.4	74.3	67.0	56.7	63.7	135.1	134.1	129.9	133.3	127.0	131.3	CO 165.9	131.3	129.6	128.4	133.3	128.4	129.6

*) Methyl signal of methanesulfonyl group.

TABLE 2. ^{13}C-NMR CHEMICAL SHIFTS OF 2-ARYL-2-BROMOMETHYL-4-BENZOYLOXYMETHYL-1,3-DIOXOLANES (1, X=Br, Y=$OCOC_6H_5$)[b]

No.	Ar		Dioxolane ring					2-Aryl group (Ar)						Benzoyloxyl group (Y)				
			2	4	5	2-CH_2	4-CH_2	1	2	3	4	5	6	CO	1	2	3	4
30	4-FC_6H_4	cis	107.9	74.3	67.5	37.5	64.3	135.9	127.9 128.5	114.8 115.8	157.6 168.5			166.2	129.8	129.8	128.3	133.3
31		trans	108.0	76.4	67.3	38.8	63.1	135.9	127.5 128.0	114.6 115.6	157.3 168.4			165.9	129.8	129.5	128.2	133.1
32	4-ClC_6H_4	cis	107.7	74.3	67.5	37.2	64.1	134.9	127.5	128.6	139.8			166.1	129.7	129.7	128.4	133.2
33		trans	108.0	76.6	67.4	38.7	63.0	134.8	127.4	128.2	138.7			166.1	130.9	129.5	128.3	133.2
34	4-BrC_6H_4	cis	107.8	74.3	67.5	37.2	64.1	138.4	127.9	131.5	123.3			166.1	131.1	129.7	128.4	133.6
35		trans	108.0	76.5	67.3	38.6	62.8	139.1	127.6	131.4	123.0			165.9	131.4	129.9	128.6	133.4
36	2,4-$Cl_2C_6H_3$	cis	108.0	74.5	67.7	35.4	64.1	135.4	133.2	129.4	133.0	126.9	131.1	166.4	131.3	129.4	128.2	133.2
37		trans	108.0	76.4	67.1	36.1	62.6	135.8	134.6	130.1	133.1	127.1	131.4	165.9	131.4	129.9	128.6	133.4
38	2,4-$Cl_2C_6H_3$[a] (Y=CH_3)	cis	106.7	78.1	70.3	36.0	26.1	136.2	135.1	129.9	132.8	126.7	130.9	(CH_3: 9.9)				
39		trans	106.9	79.9	70.2	36.1	25.5	136.3	135.0	129.8	132.7	126.8	130.7	(CH_3: 10.0)				

a) 2-Bromomethyl-2-(2,4-dichlorophenyl)-4-ethyl-1,3-dioxolane. b) Chemical shifts are given in terms of part per million (ppm) from TMS.

TABLE 3. ^{13}C CHEMICAL SHIFT DIFFERENCES ($\Delta\delta=\delta_{trans}-\delta_{cis}$) OF 2-ARYL-2-BROMOMETHYL-4-BENZOYLOXYMETHYL-1,3-DIOXOLANES

No. of compd		Ar	Carbon atom				
trans	cis		4-CH_2	4	5	2	2-CH_2
31	30	4-FC_6H_4	−1.2	+2.1	−0.2	+0.1	+1.3
33	32	4-ClC_6H_4	−1.1	+2.3	−0.1	+0.3	+1.5
35	34	4-BrC_6H_4	−1.3	+2.0	−0.2	+0.2	+1.4
37	36	2,4-$Cl_2C_6H_3$	−1.5	+1.9	−0.6	0.0	+0.7
39	38	2,4-$Cl_2C_6H_3$ (Y=CH_3)	−0.6	+1.8	−0.1	+0.2	+0.1
26	25	2,4-$Cl_2C_6H_3$ (X=CHN_4) (Y=CH_3)	−0.4	+1.1	−0.3	0.0	+0.2

given in Table 2. These bromides are the intermediates for the syntheses of the compounds in Table 1, and their stereochemistry is very important in the pharmaceutical purpose.

The assignment of the dioxolane spectra in Tables 1 and 2 was carried out according to the method cited in the literatures on simple dioxolanes.[5,6] Quite naturally, the chemical shifts of methylene carbon atom on 4-carbon atom (4-CH_2) are affected predominantly by the oxygen containing substituent (Y) on it and that on 2-carbon atom (2-CH_2) by the nature of the azole moiety. The effect by the substituent Y on 4-CH_2 group is transmitted to the ring carbon atoms in an alternate way. The 4-CH_2 carbon atom attached directly to the substituent Y resonates at the lower field as the substituent becomes more electronegative *i.e.*, in the increasing δ-values in the order of OH<$OCOC_6H_5$<OSO_2CH_3. The sequence of chemical shifts is similar as to the second neighbor carbon atom(C-5), but reversed as to the neighbor carbon atom(C-4). The effect is rather long range, the order of chemical shifts being preserved even on C(2) when compared among the derivatives carrying similar heteroaromatic moiety.

The 2-CH_2 chemical shift is linearly correlated with the N-CH_3 carbon chemical shift of the corresponding *N*-methylazole reported by Roberts and co-workers.[7] The 2-CH_2 chemical shift decreases in the increasing order of acidity.[8]

Signals of azole moiety were assigned without difficulty by comparing with the spectra of the corresponding *N*-methylazoles.[7] Chemical shifts of the carbon atoms in azolyl(X) or 2-aryl group, as well as those of benzoyl or methanesulfonyl group(Y), remain constant irrespective of the substituents in other part of the molecule.

It is important to establish the method to differentiate the cis and the trans isomers of the precursor bromides **30—39**. For this purpose. ^{13}C-NMR spectra of these bromides (in Table 2) were carefully examined. The difference in chemical shifts between the cis and the trans isomers ($\Delta\delta$) is given in Table 3. Without exception, the $\Delta\delta$ value is negative for the 4-CH_2 and positive for 4-carbon atom of the dioxolane ring. The high field shift of the 4-CH_2 chemical shift in the trans isomer is very probably due to the anisotropy effect of the 2-aryl group located just opposite to this methylene group. Another very remarkable difference in $\Delta\delta$ is observed with the 2-CH_2 group of the 4-benzoyloxyl derivatives **30—37**. Since the effect is obscured with the 4-ethyl derivatives (**38** and **39**), the high field shift is supposed to be originated from the anisotropy effect by the benzoyl group. In conclusion, the $\Delta\delta$ values are not large but very consistent in sign, hence usable to discriminate the each diastereoisomer.

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