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Study of the stereoisomeric composition of biologically active substituted 1-[(1,3-dioxolan-4-yl)methyl]-1*H*-1,2,4-triazoles and 1-[(1,3-dioxolan-4-yl)methyl]-1*H*-imidazoles by NMR spectroscopy techniques

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Abstract

Substituted 1-[(1,3-dioxolan-4-yl)methyl]-1*H*-1,2,4-triazoles and 1-[(1,3-dioxolan-4-yl)methyl]-1*H*-imidazoles possessing various biological activities were studied by ^{1}H NMR and 2D ^{1}H-^{1}H NMR spectroscopy techniques to determine their stereoisomeric composition. It was established that the predominant components of the mixture are *E*-isomers, the content of which is influenced by substituents at C^2 atom of dioxolan ring and steric factors.

Keywords:diastereomers, 1,3-dioxolane, imidazole, NOESY, 1,2,4-triazole.

INTRODUCTION

The earlier synthesized substituted 1-[(1,3-dioxolan-4-yl)methyl]-1*H*-1,2,4-triazoles and 1-[(1,3-dioxolan-4-yl)methyl]-1*H*-imidazoles demonstrated a wide range of biological activities: mainly fungicidal [1-12] and antimycotic [10, 11], as well as antimycobacterial [13], growth-regulating [14,15], antiradical [16], antibacterial [17], cytotoxic [18].

Well known that stereoisomers of related fungicidal agent propiconazole exhibit the different fungicidal activity [19]. Since the 1-[(1,3-dioxolan-4-yl)methyl]-1*H*-azoles have two optical centers, they are found in a mixture of two pairs of stereoisomers. The study of the quantitative stereoisomeric composition of biologically active compounds is of interest.

MATERIALS AND METHODS

^{1}H NMR spectra and 2D ^{1}H-^{1}H NMR spectra were recorded on Bruker AM-300 instrument (300.13 MHz), internal standard Me_4Si. The NMR solvents used were $CDCl_3$ and DMSO-d_6.

The test compounds were synthesized in two stages. 4-Chloromethyl-1,3-dioxolanes were obtained in quantitative yields by condensation of ketones (alkanophenones, benzophenones, benzylphenylketones, dibenzylketones) with glyceryl monochlorohydrin by boiling in benzene with azeotropic distillation of water under the conditions of *p*-toluenesulfonic acid catalysis. The earlier synthesized substituted 1-[(1,3-dioxolan-4-yl)methyl]-1*H*-1,2,4-triazoles and 1-[(1,3-dioxolan-4-yl)methyl]-1*H*-imidazoles were prepared with average yields by alkylation of 1,2,4-triazole and imidazole sodium salts with 4-chloromethyl-1,3-dioxolanes while boiling in DMF. Synthesis techniques, as well as a detailed description of the proton nuclear magnetic resonance (^{1}H NMR) spectra of the test compounds are presented in [1-6, 13, 16-18].

The structure of the test compounds is shown in **Fig. 1** and in **Table 1**.

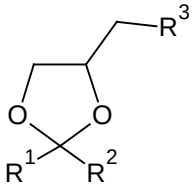

Fig. 1

RESULTS AND DISCUSSION

^{1}H NMR spectra of 1-[(1,3-dioxolan-4-yl)methyl]-1*H*-1,2,4-triazoles, 1-[(1,3-dioxolan-4-yl)methyl]-1*H*-imidazoles and 4-chloromethyl-1,3-dioxolanes show characteristic signals of 2,2,4-trisubstituted dioxolane: in the ranges of 3.56–3.75 and 3.78–3.98 ppm, two doublets of doublets (or multiplets) of methylene protons of the dioxolane ring are observed, in the range of 4.05–4.39 ppm, two doublets of doublets (or multiplets) of azolylmethyl group are found, and in the range of 4.41–4.56 ppm, quintet of methylene protons of the dioxolane ring is observed. The proton signals at C^3 atom of 1,2,4-triazole were observed in the region of 7.83–7.99 ppm, and at C^5 – in the region of 7.97–8.53 ppm. The proton signals in the imidazole fragment at C^4 atom were observed in the region of 7.07–7.22 ppm, at C^5 – in the region of 7.49–7.82 ppm, and at C^2 – in the weakest field, in the range of 8.15–8.54 ppm. The proposed NMR signal assignment is based on the following facts: 1) in comparison with the position of signals for the exocyclic methylene group protons in 4-chloromethyl-1,3-dioxolanes (2.91–3.74 ppm), the signals for the exocyclic methylene group of their azole derivatives (4.05–4.39 ppm) are shifted to the weak field at ~0.65–1.15 ppm. The position of signals for the endocyclic methylene group protons of 1,3-dioxolane, the electronic effect on which after substitution should be significantly lower, since it is further away from the reaction center, changes less significantly: in the range of ~0.2–0.3 ppm (3.75–4.28 ppm before substitution, and 3.56–3.98 ppm after substitution). 2) The 2D ^{1}H-^{1}H NMR spectra (*NOESY*) of symmetrically substituted derivatives (whose spectra do not have signal doublets) show: cross peaks reflecting the interaction between the proton H(5) of 1,2,4-triazole substituent and both protons of the exocyclic methylene group located closer to it, which is able to freely rotate around the σ-bond. The intensity of these cross peaks significantly exceeds the intensity of the cross-peak between the 1,2,4-triazole substituent proton H(5) and only one of the endocyclic methylene group protons, which do not have the possibility of free rotation.

In the ^{1}H NMR spectra of synthesized substituted 1-[(1,3-dioxolan-4-yl)methyl]-1*H*-1,2,4-triazoles, 1-[(1,3-dioxolan-4-yl)methyl]-1*H*-imidazoles and 4-chloromethyl-1,3-dioxolanes having different substituents at 2nd position of 1,3--dioxolane ring, a multiple doublet of signals was observed, indicating that the compounds are in a mixture of diastereomers analogically [20]. It was not possible to assign all the signals to both

stereoisomeric pairs in all cases, since the signals represented overlapping complex multiplets. The spectra of 4-chloromethyl-1,3-dioxolanes for different stereoisomeric pairs, in most cases, showed multiplets with similar chemical shift values. In a number of cases, the content of stereoisomers for 1-[(1,3-dioxolan-4-yl)methyl]-1*H*-1,2,4-triazoles and 1-[(1,3-dioxolan-4-yl)methyl]-1*H*-imidazoles could be determined only by the ratio of proton signals appeared as pairs of singlets at C^3 or C^5 atoms of 1,2,4-triazole, in most cases of imidazole used ratio of singlets at C^2,C^4, C^5 atoms.

^{1}H NMR spectra of the chloromethyl and azole derivatives of alkanophenones show a multiple doublet of signals for virtually all compounds, in contrast to benzophenone derivatives, for which, obviously, various substitutions in two aromatic rings have a significantly smaller effect on the electronic and spatial structure of the whole molecule (with the exception of *ortho*-substitution).

There was no significant difference or regularities in the change in the ratio of stereoisomers during the transition from 4-chloromethyl-1,3-dioxolanes to their azole derivatives (**Table 2**).

Table 1. Structure of substituted 1-[(1,3-dioxolan-4-yl)methyl]-1*H*-1,2,4-triazoles, 1-[(1,3-dioxolan-4-yl)methyl]-1*H*-imidazoles and 4-chloromethyl-1,3-dioxolanes

№	R^1	R^2	R^3	№	R^1	R^2	R^3
1a	C_6H_5	CH_3	Cl	**10a**	4-ClC_6H_4	*n*-C_7H_{15}	Cl
1b	C_6H_5	CH_3	Trz	**10b**	4-ClC_6H_4	*n*-C_7H_{15}	Trz
2a	4-ClC_6H_4	CH_3	Cl	**10c**	4-ClC_6H_4	*n*-C_7H_{15}	Im
2b	4-ClC_6H_4	CH_3	Trz	**11a**	3,4-$Cl_2C_6H_3$	*n*-C_9H_{19}	Cl
3a	2,4-$Cl_2C_6H_3$	CH_3	Cl	**11b**	3,4-$Cl_2C_6H_3$	*n*-C_9H_{19}	Trz
3b	2,4-$Cl_2C_6H_3$	CH_3	Trz	**11c**	3,4-$Cl_2C_6H_3$	*n*-C_9H_{19}	Im
4a	4-cyclo$C_6H_{11}C_6H_4$	*n*-C_3H_7	Cl	**12a**	4-ClC_6H_4	2,4-$Cl_2C_6H_3$	Cl
4b	4-cyclo$C_6H_{11}C_6H_4$	*n*-C_3H_7	Trz	**12b**	4-ClC_6H_4	2,4-$Cl_2C_6H_3$	Trz
5a	3,4-$CH_3C_6H_3$	*n*-C_3H_7	Cl	**12c**	4-ClC_6H_4	2,4-$Cl_2C_6H_3$	Im
5b	3,4-$CH_3C_6H_3$	*n*-C_3H_7	Trz	**13a**	4-FC_6H_4	4-$ClC_6H_4CH_2$-	Cl
5c	3,4-$CH_3C_6H_3$	*n*-C_3H_7	Im	**13b**	4-FC_6H_4	4-$ClC_6H_4CH_2$-	Trz
6a	4-ClC_6H_4	*n*-C_4H_9	Cl	**13c**	4-FC_6H_4	4-$ClC_6H_4CH_2$-	Im
6b	4-ClC_6H_4	*n*-C_4H_9	Trz	**14a**	4-BrC_6H_4	4-$ClC_6H_4CH_2$-	Cl
6c	4-ClC_6H_4	*n*-C_4H_9	Im	**14b**	4-BrC_6H_4	4-$ClC_6H_4CH_2$-	Trz
7a	4-ClC_6H_4	*n*-C_5H_{11}	Cl	**14c**	4-BrC_6H_4	4-$ClC_6H_4CH_2$-	Im
7b	4-ClC_6H_4	*n*-C_5H_{11}	Trz	**15a**	4-(*n*-$C_6H_{13}S)C_6H_4$	4-$ClC_6H_4CH_2$-	Cl
7c	4-ClC_6H_4	*n*-C_5H_{11}	Im	**15b**	4-(*n*-$C_6H_{13}S)C_6H_4$	4-$ClC_6H_4CH_2$-	Trz
8a	4-ClC_6H_4	*n*-C_6H_{13}	Cl	**15c**	4-(*n*-$C_6H_{13}S)C_6H_4$	4-$ClC_6H_4CH_2$-	Im
8b	4-ClC_6H_4	*n*-C_6H_{13}	Trz	**16a**	4-$ClC_6H_4CH_2$-	4-$ClC_6H_4CH_2$-	Cl
9a	4-ClC_6H_4	*cyclo*C_6H_{11}	Cl	**16b**	4-$ClC_6H_4CH_2$-	4-$ClC_6H_4CH_2$-	Trz
9b	4-ClC_6H_4	*cyclo*C_6H_{11}	Trz	**16c**	4-$ClC_6H_4CH_2$-	4-$ClC_6H_4CH_2$-	Im
9c	4-ClC_6H_4	*c*-C_6H_{11}	Im				

Trz = 1*H*-1,2,4-triazolyl; Im = 1*H*-imidazolyl

Table 2.Diastereomeric ratio for substituted 1-[(1,3-dioxolan-4-yl)methyl]-1*H*-1,2,4-triazoles, 1-[(1,3-dioxolan-4-yl)methyl]-1*H*-imidazoles and 4-chloromethyl-1,3-dioxolanes

№	Diastereomeric ratio Z:E	№	Diastereomeric ratio Z:E	№	Diastereomeric ratio Z:E	№	Diastereomeric ratio Z:E
1a	0.32:0.68	**5a**	0.48:0.52	**9a**	0.32:0.68	**13a**	0.50:0.50
1b	0.34:0.66	**5b**	0.54:0.56	**9b**	0.32:0.68	**13b**	0.33:0.67
		5c	0.44.0.66	**9c**	0.34:0.66	**13c**	0.30:0.70
2a	0.41:0.59	**6a**	0.44:0.56	**10a**	0.33:0.67	**14a**	0.39:0.61
2b	0.35:0.65	**6b**	0.21:0.79	**10b**	0.45:0.55	**14b**	0.37:0.63
		6c	0.38:0.62	**10c**	0.32:0.68	**14c**	0.24:0.76
3a	0.37:0.63	**7a**	0.33:0.67	**11a**	0.27:0.73	**15a**	0.26:0.74
3b	0.36:0.64	**7b**	0.30:0.70	**11b**	0.19:0.81	**15b**	0.50:0.50
		7c	0.37:0.63	**11c**	0.43:0.57	**15c**	0.38:0.62
4a	0.29:0.71	**8a**	0.42:0.58	**12a**	0.43:0.57	**16a**	0.32:0.68
4b	0.13:0.87	**8b**	0.42:0.58	**12b**	0.21:0.79	**16b**	0.20:0.80
				12c	0.18:0.82	**16c**	0.40:0.60

For the majority of both intermediate 4-chloromethyl-1,3-dioxolanes and the target azoles, there was approximately a two fold predominance of one of the pairs of stereoisomers. Assignment of the major and minor pairs of stereoisomers of **2b**, **7b** and **12b** compounds to their spatial configuration was performed with the help of the *NOESY* experiment. In each of the 2D ^{1}H-^{1}H NMR spectra of these compounds, cross peaks are observed reflecting the interaction of the triazole proton H(5) with protons of substituents at C(2) atom of the dioxolane ring. For both stereoisomeric pairs of **2b** compound, cross-peaks of the triazole substituent protons H(5) are observed: for the major pair – with protons of the smallest methyl group at C(2) of dioxolane, and for the minor pair – with *ortho*-protons of the 4-chlorophenyl substituent. A similar pattern is observed for **7b** compound, in the spectrum of which there is a cross-peak between the triazole proton H(5) and methylene protons at C (1), C (2) and C (3) of *n*-pentyl substituent. For **12b** compound having two non-equivalent aryl substituents in the 2nd position of the dioxolane ring, a cross peak is observed between the triazole substituent proton signal H(5) and the *ortho*-proton signals of 4-chlorophenyl substituent for the major pair. Since the 1,2,4-triazole substituent is larger than hydrogen, in the major pair of stereoisomers it is closer to the alkyl rather than larger aryl substituent. This pair has the configuration of *E* isomer (*E* configuration), and the minor one – of *Z* isomer (*Z* configuration), respectively (**Fig.2**).

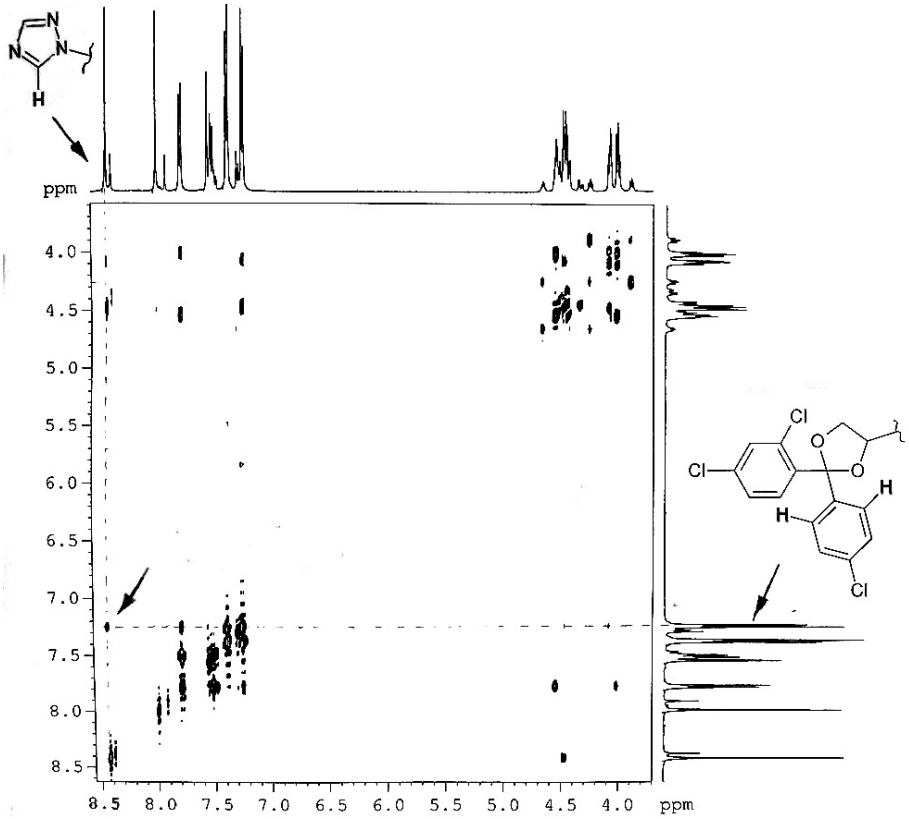

Fig. 2. Fragment of the 2D ^{1}H-^{1}H NMR spectrum for the 12b derivative.

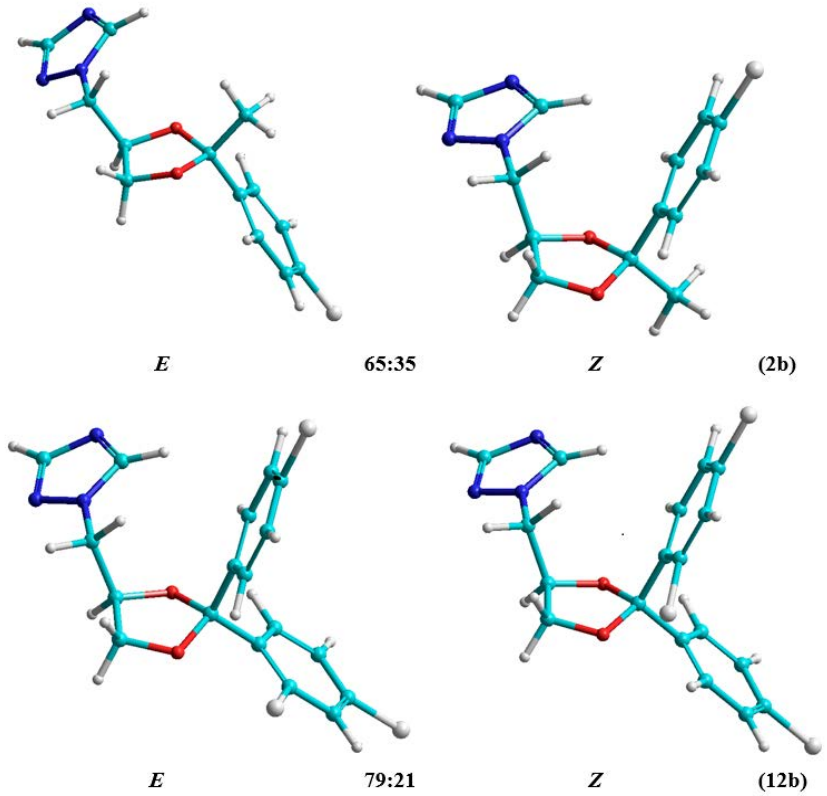

Fig. 3. Possible diastereomeric pairs for 2b and 12b derivatives.

The *E:Z* ratio of diastereomers of 2,2-disubstituted 4-(azol-1-ylmethyl)-1,3-dioxolanes varies depending on the geometric parameters of the substituent at the 2nd position of 1,3-dioxolane: for a less sterically hindered **2b** derivative of 4-chloroacetophenone, it is 1.86:1, and for the **12b** derivative, 2,4-dichlorophenyl ring of which creates the greatest steric hindrance, the *E* isomer content increases to 4.56:1 (**Fig.3**).

CONCLUSIONS

The use of NMR spectroscopy techniques allowed to determine the quantitative ratio of stereoisomers of 1-[(1,3-dioxolan-4-yl)methyl]-1*H*-1,2,4-triazoles, 1-[(1,3-dioxolan-4-yl)methyl]-1*H*-imidazoles and 4-chloromethyl-1,3-dioxolanes. These data will be useful in determining the effect of the geometric structure of isomers on their biological activity.

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