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Preparation and Spectral Properties of 2-(2,4-Dichlorophenyl)-2-(1,2,3,5-tetrazol-1-ylmethyl)-1,3-dioxolan-4-ylmethanol and Its Benzoate and Methanesulfonate

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The title compounds were prepared by nucleophilic substitution by tetrazole anion of the corresponding bromide (**1**), followed by hydrolysis and methanesulfonylation. The site of alkylation of the tetrazole anion was determined by comparison of the ^{13}C-nuclear magnetic resonance spectrum with those of *N*-methyltetrazoles.

Keywords——azolyldioxolane; methanesulfonylation; ^{13}C-NMR; tetrazole; alkylation

4-(Substituted aryl)-2-(1-imidazolyl)-1,3-dioxolanes have been shown to have antifungal and bactericidal activities.[1)] In connection with our recent investigations[2)] on analogous compounds carrying pyrazolyl, imidazolyl and triazolyl groups, a new synthesis of the title compounds was carried out in order to examine the products for such activities.

Results and Discussion

The synthesis was carried out as follows. The starting *cis*-bromide (**1**)[1,3)] was prepared from 2-(2,4-dichlorophenyl)-2-methyl-1,3-dioxolan-4-ylmethanol. The *cis*-bromide (**1**) was employed because the *cis* azolyl derivative shows higher antifungal activities than the *trans* isomer.[4)] The tetrazolyl moiety was introduced by the condensation of the bromide **1** with the sodio derivative of tetrazole. The benzoyl group of **2** was removed by alkaline hydrolysis, providing the tetrazolyl alcohol (**3**). Then, the alcohol **3** was esterified with methanesulfonyl chloride in the presence of pyridine as a base.

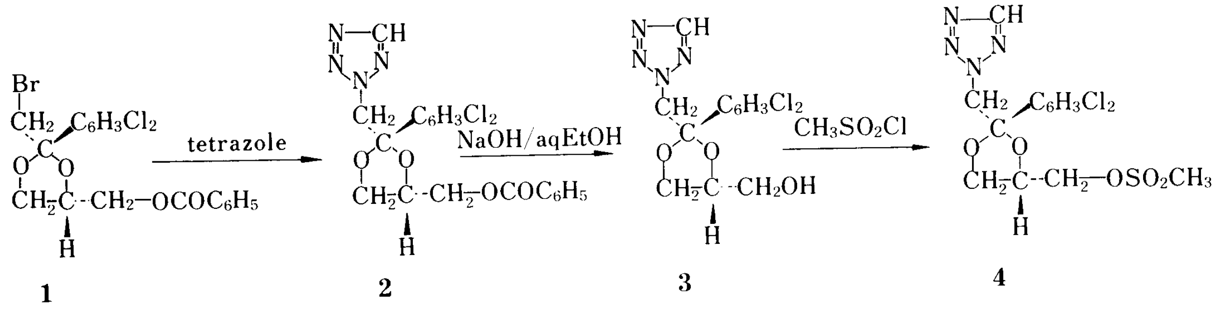


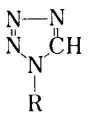
Chart 1. Syntheses of the Tetrazolylmethyldioxolanes **2**—**4**

The structures of the tetrazolyl derivatives **2**—**4** were determined by spectroscopic methods. The ^{1}H- and ^{13}C-nuclear magnetic resonance (NMR) data for these compounds are given in Table I. Since tetrazole is tautomeric, interconverting between 1*H*- (**5′**) and 2*H*-

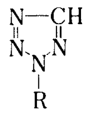
Table I. ^{1}H- and ^{13}C-NMR Data (δ/ppm from TMS) for the Tetrazolyldioxolanes (**2**—**4**)$^{a)}$

Compd. No.		Dioxolane ring					Tetrazole	2,4-Dichlorophenyl			Other ^{1}H signals
		2	4	5	2-CH_2	4-CH_2	4	3	5	6	
2	^{1}H	—	4.34	3.80 3.90	5.29	4.20	8.36	7.51	7.19	7.50	Ph 7.99—7.44
	^{13}C	107.4	74.3	67.0	56.7	63.7	152.7	$^{a)}$			
3	^{1}H	—	4.20	3.38 3.70	5.32	3.88	8.55	7.50	7.27	7.57	OH 3.28 (br)
	^{13}C	106.9	77.1	66.6	56.7	61.6	152.8	$^{a)}$			
4	^{1}H	—	4.34	3.73 3.92	5.30	4.00	8.55	7.50	7.27	7.55	CH_3 3.12
	^{13}C	107.9	74.0	67.9	56.8	66.3	152.9	$^{a)}$			

a) ^{13}C-NMR spectra were reported in ref. 6. Only the signals necessary for the discussion are given in this table.



5′: R = H
5 : R = CH_3



6′: R = H
6 : R = CH_3

form (**6′**), it has two methyl derivatives, namely 1-methyl-1,2,3,4-tetrazole (**5**) and 1-methyl-1,2,3,5-tetrazole (**6**). In the case of the condensation of the bromide **1** with the sodio derivative of tetrazole, the tetrazolate anion is also ambident, having the possibility to react with the bromide at the nitrogen atom at either the 1- or 2-position of the tetrazole ring. The site of alkylation was unambiguously determined by comparing the ^{13}C-NMR spectra with those of *N*-methyltetrazoles **5** and **6**, whose ring ^{13}C atoms resonate at 144.2 and 153.4 ppm downfield from tetramethylsilane (TMS) standard, respectively. Since the ^{13}C resonance signals of carbon atoms in similar circumstances usually appear within a very narrow range of chemical shift, the alkylation of the tetrazolate anion is considered to take place on the 2-nitrogen atom, producing 1,2,3,5-tetrazolyl derivatives. This conclusion is supported by the linear relationship between δ_{CH_3} of *N*-methylazoles$^{5)}$ and δ_{CH_2} of these and related derivatives of 2-azolylmethyl-1,3-dioxolanes.$^{6)}$

Mass spectra (MS) did not provide conclusive evidence regarding the structures. Molecular ion peaks could not be observed in the MS of these compounds. The $[M-83]^+$ peaks are the most intense with all of these tetrazolyl derivatives, and are assigned to the cations formed by elimination of a tetrazolylmethyl fragment from the molecular ions.

Experimental

Measurement of the spectra——^{1}H- and ^{13}C-NMR spectra were recorded on JEOL 4H-100 and FX-90Q spectrometers, respectively, in $CDCl_3$. MS were measured with a Hitachi RMU-6L or a Shimadzu LKB-9000B mass spectrometer usually by direct insertion of the samples.

***cis*-4-Benzoyloxymethyl-2-(2,4-dichlorophenyl)-2-(1,2,3,5-tetrazol-1-ylmethyl)-1,3-dioxolane (2)**——A solution of 1*H*-tetrazole (0.77 g, 0.011 mol) in anhydrous *N*,*N*-dimethylformamide (DMF, 8 ml) was added dropwise to a stirred slurry of 60% sodium hydride (0.44 g, 0.011 mol) in anhydrous DMF (8 ml). The mixture was kept stirred until the evolution of gaseous hydrogen was completed. Then the reaction mixture was heated to 80°C. A solution of *cis*-4-benzoyloxy-2-bromomethyl-2-(2,4-dichlorophenyl)-1,3-dioxolane (**1**) (4.46 g 0.01 mol) and 18-crown-6 (0.5 g, 0.004 mol) in anhydrous DMF (10 ml) was added dropwise to the mixture. the whole was heated gradually to 143 °C and kept at that temperature with efficient stirring for 24 h. the reaction mixture was then cooled and treated with water (*ca.* 50 ml). The mixture was extracted with CH_2Cl_2. The extract was washed with water, and dried over anhydrous $MgSO_4$. The solvent was evaporated off and the residual oil was purified by column chromatography on silica gel. The eluate was crystallized from EtOH to give the benzoate (**2**) (0.75 g, 16%) as colorless needles, mp 81—82 °C. *Anal.* Calcd for $C_{19}H_{16}Cl_2N_4O_4$: C, 52.43; H, 3.71; N, 12.87. Found: C, 52.46; H, 3.62; N, 12.81.

***cis*-2-(2,4-Dichlorophenyl)-2-(1,2,3,5-tetrazol-1-ylmethyl)-1,3-dioxolan-4-ylmethanol (3)**——A solution of **2** (3.6 g, 0.0083 mol) in dioxane (50 ml) was mixed with a solution of sodium hydroxide (6.4 g) in aqueous ethanol (H_2O 19 ml and EtOH 15 ml). The mixture was heated under reflux for 1 h. Separation and purification of the product were carried out in the same way as in the case of **2**. Elution with $CHCl_3$ gave **3** (2.2 g, 77%) as a viscous colorless oil.

***cis*-2-(2,4-Dichlorophenyl)-4-methanesulfonyloxymethyl-2-(1,2,3,5-tetrazol-1-ylmethyl)-1,3-dioxolane (4)**——Methanesulfonyl chloride (0.75 g, 0.0049 mol) was added dropwise to an ice-cooled and stirred solution of the alcohol **3** (1.5 g, 0.0045 mol) in pyridine (7.5 ml). When the reaction had reached completion, the reaction mixture was poured into ice-water. Separation and purification of the product were carried out in the same way as in the case of **2**. The product was crystallized from EtOH to give **4** (1.75 g, 97%) as colorless prisms, mp 93—94 °C. *Anal.* Calcd for $C_{13}H_{14}Cl_2N_4O_5S$: C, 38.15; H, 3.45; N, 13.69. Found: C, 38.27; H, 3.41; N, 13.62.

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References and Notes

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3) In this paper, the terms *cis* and *trans* refer to the relative arrangement of the two methylene groups attached to the 1,3-dioxolane ring. Thus, the compounds **1**—**4** in Chart 1 are all *cis*, since the bromomethyl or azolylmethyl group on C-2 and the hydroxymethyl or acyloxymethyl group on C-4 are located on the same side of the plane of the dioxolane ring.
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