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SYNTHESIS AND STEREOCHEMISTRY OF SOME NEW 2,5-POLYSUBSTITUTED –1,3-DIOXANES

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ABSTRACT. The synthesis and the stereochemistry of some new 1,3-dioxanes bearing aliphatic, aromatic and heteroaromatic substituents in the acetal part of the dioxanic heterocycle are reported.

INTRODUCTION

In previous works, the stereochemistry of 2,5-substituted-1,3-dioxanes, exhibiting anancomeric or flipping structure, in correlation with the nature of the substituents, has been reported[1-11].

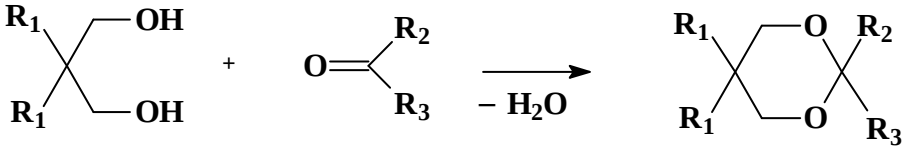
The compounds displaying identical geminal substituents or geminal substituents with very close conformational free enthalpies, show flipping structures. Their ^{1}H- and ^{13}C-NMR spectra exhibit unique signals (at mean values of the chemical shifts) for the equatorial and axial positions of the protons of the heterocycle and for the axial and equatorial positions of the protons and carbon atoms of the homomorphic groups located at positions 2 and 5.

In the case of compounds having different substituents located at the same position, the conformational equilibria are shifted towards the conformation with the group exhibiting the largest conformational free enthalpy in equatorial position. For these compounds (with anancomeric structure), the NMR spectra show different signals for the axial and equatorial protons of the ring and for the protons and carbon atoms of the similar groups located in it.

It was considered of interest to study by means of NMR spectra, the stereochemistry of some new 1,3-dioxane derivatives, bearing many types of substituents at the positions 2- and 5.

RESULTS AND DISCUSSION

New 2,5-substituted-1,3-dioxanes have been obtained (Scheme 1) by the condensation reaction of 2,2-substituted-1,3-propandiols with aldehydes and ketones:

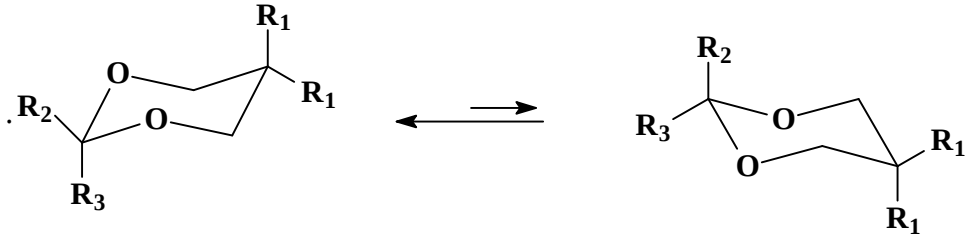


$R_1 = CH_3$	$R_2 =$	H	$R_3 =$	$(CH_3)_2CH$	**1**
				C_6H_{11}	**2**
				C_5H_4N	**3**
				$C_5H_4N^+C_2H_5$	**4**
				C_4H_4N	**5**
				$(CH_3)_2CBr$	**6**
$R_1 = CH_3$	$R_2 =$	CH_3	$R_3 =$	$(CH_3)_2CH$	**7**
$R_1 = COOC_2H_5$		CH_2Br		C_6H_5	**8**
		CH_2Cl		CH_2Cl	**9**
		CH_2Br		CH_2Br	**10**
		$CH_2C_6H_5$		$CH_2C_6H_5$	**11**

Scheme 1

These compounds exhibit anancomeric or flipping structures, in correlation with the nature of the substituents.

Thus, the conformational analysis for compounds **1**-**8** shows anancomeric structures. At room temperature, the conformational equilibria are shifted towards the conformation A, in which the substituent with the largest conformational enthalpy (R_2) is in the equatorial position (Scheme 2):



A B

Scheme 2

The NMR spectra of these compounds exhibit different signals for the axial and equatorial protons at the 4,6-positions of the heterocyclic ring as well as for the protons and for the carbon atoms of axial and equatorial methyl and ethyloxycarbonyl groups located at position 5.

The ^{1}H and ^{13}C-NMR data for compounds **1**-**8** are ilustrated in Tables 1 and 2.

Table 1

^{1}H- NMR data for compounds **1**-**8**

Compound	**^{1}H-NMR**			
	4,6-H_{eq}	**4,6-H_{ax}**	**5-CH_{3eq}**	**5-CH_{3ax}**
1	3.43	3.12	0.33	1.12
2	3.45	3.13	0.32	1.14
3	3.50	3.29	0.28	1.21
4	3.87	3.78	0.80	1.18
5	3.44	3.18	0.33	1.14
6	3.37	3.03	0.22	1.05
7	3.48	3.24	0.54	0.97
8	4.84	4.04	-	-

Table 2

^{13}C-NMR data for compounds **1**-**8**

Compound	**^{13}C-NMR**				
	C^{2}	**$C^{4,6}$**	**C^{5}**	**5-CH_{3ax}**	**5-CH_{3eq}**
1	105.38	76.78	29.68	22.71	21.27
2	104.93	76.84	29.76	22.71	21.30
3	103.03	77.12	29.71	22.84	21.21
4	94.95	77.59	30.45	23.03	21.47
6	105.02	77.06	29.88	22.94	21.18
7	100.75	70.18	29.28	23.06	22.42
8	99.43	64.33	23.06	-	-

As an example, the ^{1}H-NMR spectrum of compound **8** (Figure 1) shows two doublets for the protons at positions 4 and 6 ($\delta_{4,6\ eq}$ = 4.84 and $\delta_{4,6\ ax}$ = 4.04 ppm), two quartets (δ_{eq} = 4.16 and δ_{ax} = 3.60 ppm) belonging to the protons of the methylene groups and also two triplets (δ_{eq} = 1.05, δ_{ax} = 0.55 ppm) for the methyl groups belonging to the axial and equatorial ester groups of 5-position. The spectrum also exhibits a singlet (δ = 3.30 ppm) associated with the methylene protons of the CH_2Br substituent and a complex signal at 7-7.34 ppm belonging to the protons of the phenyl group.

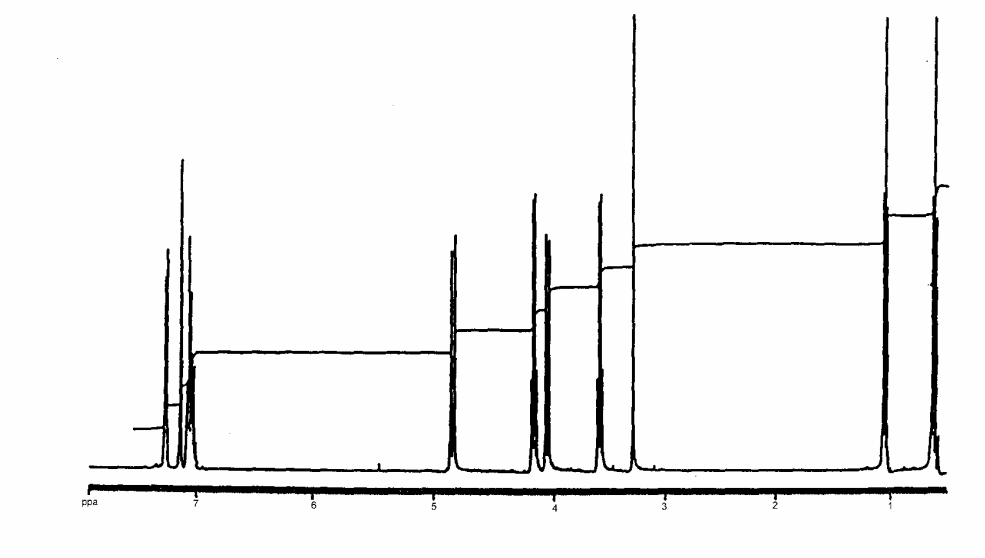
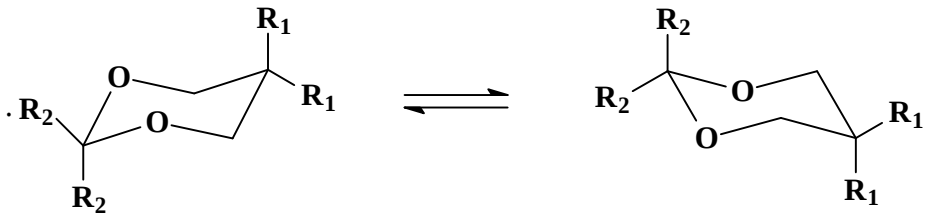


Fig.1. ^{1}H-NMR Spectrum of compound **8**

The conformational analysis shows flipping structures for compounds **9**-**11**. These compounds exhibit, at room temperature, a rapid inversion of the six membered ring (C D; Scheme 3):



C D

Scheme 3

The NMR spectra of these compounds exhibit unique signals (at the mean values of the chemical shifts) for the axial and equatorial positions of the protons of the ring and of the similar groups located in it (Table 3).

Table 3

^{1}H-NMR data for compounds **9**-**11**

Compound	**^{1}H-NMR**			
	4,6-H	**CH_2Cl**	**CH_2Br**	**CH_2Ph**
9	4.14	3.66	-	-
10	4.10	-	3.52	-
11	4.50	-	-	2.89

The ^{1}H-NMR spectrum of compound **11** (Figure 2) shows a singlet at δ = 4.50 ppm corresponding to the protons at the positions 4 and 6 of the heterocycle, a quartet (δ = 3.81 ppm) for the methylene group and a triplet (δ = 0.83 ppm) for the protons of the methyl group of the ester groups located at the 5-position. In the spectrum also appears a complex signal (δ = 7-7.25 ppm) due to the aromatic protons and a singlet at δ = 2.89 ppm for the methylene protons of the benzyl groups.

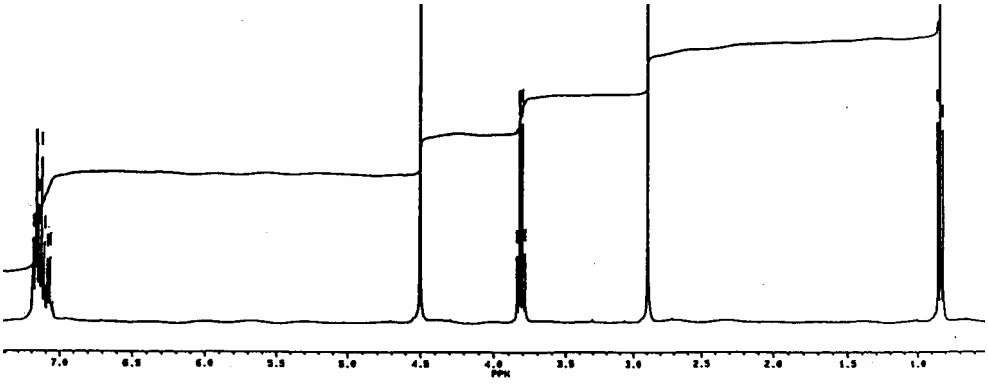


Fig.2. ^{1}H-NMR Spectrum of compound **9**

CONCLUSIONS

The stereochemistry of 1,3-dioxane derivatives have been determined by NMR investigations. The flipping or the anancomeric structure of the compounds has been deduced from the complexity of NMR spectra. The presence in the spectra of distinct signals for axial and equatorial positions have been associated with anancomeric structures, whereas the spectra with unique signals correspond to flipping structures.

EXPERIMENTAL

^{1}H-and ^{13}C-NMR spectra were recorded at room temperature, using C_6D_6 as solvent, in 5 mm tubes, on a Bruker AM 400 spectrometer, operating at 400 MHz for protons and at 100 MHz for carbon atoms. Melting points were measured with Electrothermal melting point apparatus and are uncorrected.

*New compounds **1**-**11**, general procedure:*

Equimolecular amounts of 1,3-diol (0.1 mol) and carbonyl compound, with catalytic amount (0.1 g) of *p*-toluenesulphonic acid were solved in 200 ml of benzene. The mixture was refluxed and the water was removed using a Dean-Stark trap. When 80% of the theoretical amount of water was separated, the mixture was cooled at room temperature and then was neutralized with CH_3COONa powder in excess (0.2 g). The mixture was wash twice with 100 ml of water. After drying (with Na_2SO_4) the benzene was removed and the 1,3-dioxanic compound was purified by vacuum distillation (1-2 mm col. Hg) or by crystallisation from ethanol.

2-*i*-Propyl-5,5-dimethyl-1,3-dioxane **1**

Liquid, b.p. = 49-50 ^{0}C (1 mm col. Hg). Yield 80%. $C_9H_{18}O_2$, found: C 69.02, H 11.19; required: C 68.35, H 11.39%

^{1}H-NMR (C_6D_6): δ 0.33 [3H, s, 5-CH_{3eq}], 1.05 [6H, d, J = 6.8 Hz, 2-$CH(CH_3)_2$], 1.12 [3H, s, 5-CH_{3ax}], 1.93 [H, dh, J = 4.5 Hz, J'= 6.8 Hz, 2-$CH(CH_3)_2$], 3.12 [2H, d, J = 11.0 Hz, 4,6-H_{ax}], 3.43 [2H, d, J = 11.0 Hz, 4,6-H_{eq}], 4.05 [H, d, J = 4.5 Hz, 2-H_{ax}]

^{13}C-NMR (C_6D_6): δ 16.84 [2-$CH(\underline{C}H_3)_2$], 21.27 (5-CH_{3eq}}, 22.71 (5-CH_{3ax}), 29.68 (C^5), 32.75 [2-$\underline{C}H(CH_3)_2$], 76.78 ($C^{4,6}$), 105.38 (C^2)

2-Cyclohexyl-5,5-dimethyl-1,3-dioxane **2**

Liquid, b.p. = 90-92 ^{0}C (1 mm col. Hg). Yield 69%. $C_{12}H_{22}O_2$, found: C 71.92, H 11.22; required: C 72.72, H 11.11%

^{1}H-NMR (C_6D_6): δ 0.32 [3H, s, 5-CH_{3eq}], 1.14 [3H, s, 5-CH_{3ax}], 1.18-1.27 [11H, m, overlapped peaks], 3.13 [2H, d, J = 11.0 Hz, 4,6-H_{ax}], 3.45 [2H, d, J = 11.0 Hz, 4,6-H_{eq}], 4.10 [H, d, J = 4.8 Hz, 2-H_{ax}]

^{13}C-NMR (C_6D_6): δ 21.30 (5-CH_{3eq}}, 22.71 (5-CH_{3ax}), 26.01, 26.69, 27.41, 42.51 (cyclohexanic ring), 29.76 (C^5), 76.84 ($C^{4,6}$), 104.93 (C^2)

2-Pyridyl-5,5-dimethyl-1,3-dioxane **3**

Liquid, b.p. = 95-96 ^{0}C . Yield %. $C_{12}H_{15}O_2N$, found: C 69.21, H 7.61, N 7.06; required: C 68.39, H 7.77, N 7.25%

^{1}H-NMR (C_6D_6): δ 0.28 [3H, s, 5-CH_{3eq}], 1.21 [3H, s, 5-CH_{3ax}], 3.29 [2H, d, J = 11.5 Hz, 4,6-H_{ax}], 3.50 [2H, d, J = 11.5 Hz, 4,6-H_{eq}], 5.65 [H, s, 2-H_{ax}], 6.62, 7.15, 7.75, 8.44 (4H, overlapped peaks, aromatic protons)

^{13}C-NMR (C_6D_6): δ 21.20 (5-CH_{3eq}}, 22.84 (5-CH_{3ax}), 29.71 (C^5), 77.12 ($C^{4,6}$), 103.03 (C^2), 120.78, 123.32, 135.87, 148.57, 158.04 (aromatic carbon atoms)

N-Ethyl, 2-(5,5-dimethyl-1,3-dioxane-2-yl) pyridinium iodine **4**

Solid, m.p. = .138^{0}C. Yield 48%. $C_{13}H_{20}O_2NJ$, found: C 43.88, H 5.89, N 3.96, J 37.23 required: C 44.69, H 5.73, N 4.01, J 36.39%

^{1}H-NMR (C_6D_6): δ 0.80 [3H, s, 5-CH_{3eq}], 1.18 [3H, s, 5-CH_{3ax}], 1.65 [3H, t, J = 7.2 Hz, N-CH_2-$\underline{C}H_3$], 3.78 [2H, d, J = 11.2 Hz, 4,6- H_{ax}], 3.87 [2H, d, J = 11.2 Hz, 4,6-H_{eq}], 5.00 [2H, q, J = 7.2 Hz, N-$\underline{C}H_2$-CH_3], 6.16 [H, s, 2-H_{ax}], 8.15, 8.28, 8.48, 9.66(4H, m, overlapped peaks, aromatic protons)

^{13}C-NMR (C_6D_6): δ 17.43 (N-CH_2-$\underline{C}H_3$), 21.47 (5-CH_{3eq}}, 23.03 (5-CH_{3ax}), 30.45 (C^5), 54.79 (N-$\underline{C}H_2$-CH_3), 77.59 ($C^{4,6}$), 94.95 (C^2)

2-Pyril-5,5-dimethyl-1,3-dioxane **5**

Liquid, b.p. = 84-86 ^{0}C . Yield 40%. $C_{10}H_{15}O_2N$, found: C 67.96, H 8.10, N 7.91; required: C 66.63, H8.28, N 7.73%

^{1}H-NMR (C_6D_6): δ 0.33 [3H, s, 5-CH_{3eq}], 1.14 [3H, s, 5-CH_{3ax}], 3.18 [2H, d, J = 11.8 Hz, 4,6-H_{ax}], 3.44 [2H, d, J = 11.8 Hz, 4,6-H_{eq}], 5.29 [H, s, 2-H_{ax}], 6.26, 6.36, 6.49 (3H, m, aromatic protons)

2-(2-Bromo-2-propyl)-5,5-dimethyl-1,3-dioxane **6**

Solid, m.p. =110-112 ^{0}C . Yield 70%. $C_9H_{17}O_2Br$, found: C 44.69, H 7.34, Br 34.71; required: C 45.37, H 7.14, Br 34.03%

^{1}H-NMR (C_6D_6): δ 0.22 [3H, s, 5-CH_{3eq}], 1.05 [3H, s, 5-CH_{3ax}], 1.77 [6H, s, $(C\underline{H}_3)_2CBr$], 3.03 [2H, d, J = 11.0 Hz, 4,6-H_{ax}], 3.37 [2H, d, J = 11.0 Hz, 4,6-H_{eq}], 4.22 [H, s, 2-H_{ax}]

^{13}C-NMR (C_6D_6): δ 21.18 (5-CH_{3eq}}, 22.94 (5-CH_{3ax}), 28.88 [($\underline{C}H_3)_2CBr$], 29.88 (C^5), 63.39 , [$(CH_3)_2\underline{C}Br$], 77.06 ($C^{4,6}$), 105.02 (C^2)

2,5,5-Trimethyl-2-*i*-Propyl-1,3-dioxane **7**

Liquid, b.p. = 68 ^{0}C Yield 55%. $C_{10}H_{20}O_2$, found: C 71.03, H 11.51; required: C 69.76, H 11.63%

^{1}H-NMR (C_6D_6): δ 0.54 [3H, s, 5-CH_{3eq}], 0.97 [3H, s, 5-CH_{3ax}], 1.06 [6H, d, J = 6.5 Hz, 2-CH($\underline{C}H_3)_2$], 1.20 [3H, s, 2-CH_{3ax}], 2.08 [H, h, J = 6.5 Hz, 2-$\underline{C}H(CH_3)_2$], 3.24 [2H, d, J = 11.0 Hz, 4,6-H_{ax}], 3.38 [2H, d, J = 11.0 Hz, 4,6-H_{eq}]

^{13}C-NMR (C_6D_6): δ 15.42 [2-CH_{3ax}], 17.10 [2-CH($\underline{C}H_3)_2$], 22.42 (5-CH_{3eq}}, 23.06 (5-CH_{3ax}), 29.98 (C^5), 36.21 [2-$\underline{C}H(CH_3)_2$], 70.18 ($C^{4,6}$), 100.75 (C^2)

2-Bromomethyl-5,5-di(ethyloxycarbonyl)-2-phenyl-1,3-dioxane **8**

Liquid, b.p. = 181^{0}C. Yield 62% $C_{17}H_{21}O_6Br$, found: C 50.93, H 5.16, Br 20.54; required: C 50.74, H 5.22, Br 20.15%

^{1}H-NMR (C_6D_6): δ 0.55 [3H, t, J = 7.1 Hz, 5-$COOCH_2C\underline{H}_{3ax}$], 1.05 [3H, t, J = 7.1 Hz, 5-$COOCH_2C\underline{H}_{3eq}$], 3.30 [2H, s, 2-$CH_2Br$], 3.60 [2H, q, J = 7.1 Hz, 5-$COO\underline{C}H_2CH_{3ax}$], 4.04 [2H, d, J = 11.3 Hz, 4,6-H_{ax}], 4.16 [2H, q, J = 7.1 Hz, 5-$COO\underline{C}H_2CH_{3eq}$], 4.84 [2H, d, J = 11.3 Hz, 4,6-H_{eq}], 7-7.34 [5H, m]

^{13}C-NMR (C_6D_6): δ 13.58 (5-$COOCH_2\underline{C}H_{3ax}$), 14.11 (5-$COOCH_2\underline{C}H_{3eq}$), 39.96 ($CH_2Br$), 53.37 ($C^5$), 61.66 (5-$COO\underline{C}H_2CH_{3ax}$), 62.12 (5-$COO\underline{C}H_2CH_{3eq}$), 64.33 ($C^{4,6}$), 99.43($C^2$), 128.66, 129.11, 129.19, 135.94 (aromatic carbon atoms)

2,2-Di(chloromethyl)-5,5-di(ethyloxycarbonyl)-1,3-dioxane **9**

Liquid, b.p. = 147-148^{0}C. Yield 64%. $C_{12}H_{18}O_6Cl_2$, found: C 44.59, H 5.62,Cl 21.13; required: C 43.77, H 5.47, Cl 21.58%

^{1}H-NMR ($CDCl_3$): δ 1.15 [6H, t, J = 7.0 Hz, 5-$COOCH_2C\underline{H}_3$], 3.66 [4H, s, 2-CH_2Cl], 4.14 (4H, s, 4,6-H), 4.20 [4H, q, J = 7.0 Hz, 5-$COO\underline{C}H_2CH_3$]

2,2-Di(bromomethyl)-5,5-di(ethyloxycarbonyl)-1,3-dioxane **10**

Liquid, b.p. = 180-181^{0}C. Yield 64%. $C_{12}H_{18}O_6Br_2$, found: C 35.17, H4.22, Br 38.04; required: C 34.28, H 4.28, Br 38.57%

^{1}H-NMR (CCl_4): δ 1.15 [3H, t, J = 7.0 Hz, 5-$COOCH_2C\underline{H}_3$], 3.52 [4H, s, 2-CH_2Br], 4.10 (4H, s, 4,6-H), 4.12 [2H, q, J = 7.0 Hz, 5-$COO\underline{C}H_2CH_3$]

2,2-Dibenzyl-5,5-di(ethyloxycarbonyl)-1,3-dioxane **11**

Solid, m.p. = 61-62 ^{0}C. Yield 72%. $C_{24}H_{28}O_6$, found: C 71.30, H 6.67; required: C 69.90, H 6.79%

^{1}H-NMR (CCl_4): δ 0.86 [3H, t, J = 7.1 Hz, 5-$COOCH_2C\underline{H}_3$], 2.89 [4H, s, 2-CH_2Ph], 3.81 [4H, q, J = 7.0 Hz, 5-$COO\underline{C}H_2CH_3$], 4.50 (4H, s, 4,6-H), 7-7.25 (10H, overlapped peaks)

^{13}C-NMR (CCl_4): δ 13.81 ($COOCH_2\underline{C}H_3$), 54.03 (C^5), 61.66 ($COO\underline{C}H_2CH_3$), 62.58 ($C^{4,6}$), 101.04(C^2), 126.47, 128.01, 131.12, 135.59 (aromatic carbon atoms), 167.69 ($COOCH_2CH_3$)

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