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Dedicated to Professor Ionel Haiduc
on the occasion of his 65th birthday

SYNTHESIS AND STEREOCHEMISTRY OF SOME NEW 2,4-SUBSTITUTED-1,3-DIOXANES

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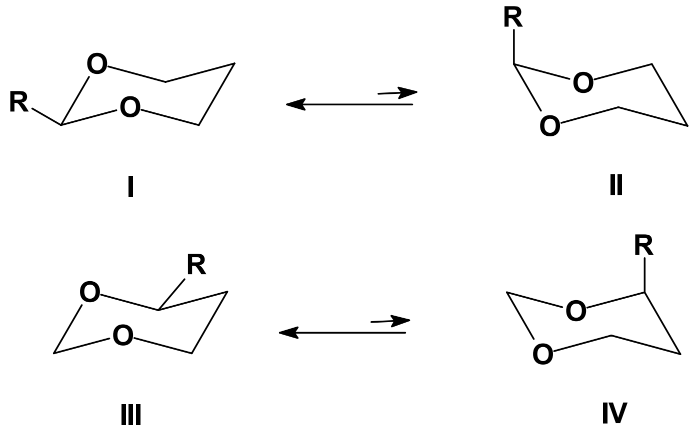
ABSTRACT. The stereoselective synthesis and the anancomeric behavior of new 1,3-dioxane derivatives bearing a methyl group at the position 4 and various substituents at position 2 are reported.

INTRODUCTION

The investigations on the stereochemistry of 1,3-dioxane derivatives revealed the high preference of alkyl and aryl groups for the equatorial orientation either at position 2 or at position 4.[1-5] The A-value (free conformational enthalpy) of the same substituent is considerably higher at position 2 than at position 4, but usually in both cases it is high enough to determine the anancomeric behavior of the compound (Table 1, Scheme 1). On the other side due to peculiar rotameric behavior alkyl groups exhibit larger A-value than aromatic substituents (Table 1). It was considered of interest to investigate the conformational and configurational aspects concerning the structure of 1,3-dioxane derivatives bearing a methyl group at position 4 and various aromatic substituents at position 2.



Scheme 1

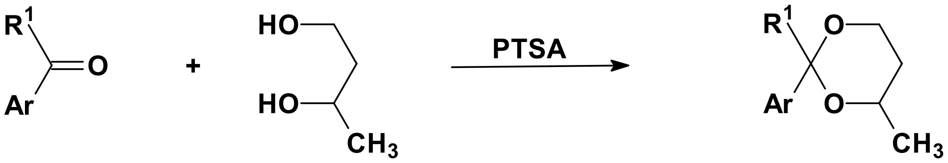
Table 1.

A-values (kcal/mol) for representative alkyl and aryl groups at positions 2 and 4.

Substituent	A-values			References
	position 2	position 4	ΔA	
Me	3.98	2.90	1.08	6,7
Et	4.04	3.00	1.04	6,8
i-Pr	4.17	3.55	0.62	6,8
Ph	3.12	2.85	0.27	6,8

RESULTS AND DISCUSSIONS

The condensation reaction of racemic 2-methyl-1,3-butanediol with several aromatic aldehyde and ketones leads to 2,4-substituted-1,3-dioxane derivatives (Scheme 2).

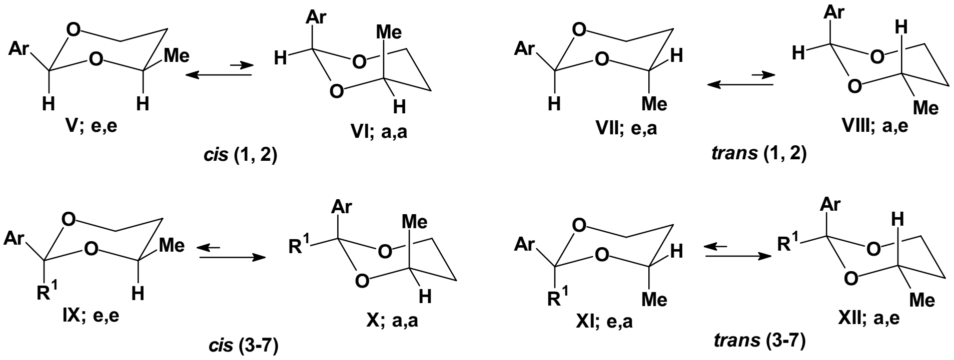


$R^1 = H$	$Ar = C_6H_5$	**1**
$R^1 = H$	$Ar = \beta\text{-}C_{10}H_7$	**2**
$R^1 = CH_3$	$Ar = C_6H_5$	**3**
$R^1 = CH_3$	$Ar = p\text{-}O_2N\text{-}C_6H_4$	**4**
$R^1 = CH_3$	$Ar = o\text{-}O_2N\text{-}C_6H_4$	**5**
$R^1 = CH_3$	$Ar = \alpha\text{-}C_{10}H_7$	**6**
$R^1 = C_2H_5$	$Ar = C_6H_5$	**7**

Scheme 2

All investigated compounds can exhibit *cis* and *trans* isomers (Scheme 3). The acetalisation reaction occurs under equilibrium conditions. *Cis* and *trans* isomers are obtained in ratios reflecting the differences of stability between these isomers. The conformational equilibrium is shifted (as proved by the investigations performed by high resolution NMR spectroscopy and by GC-MS) towards one of the isomers which is more stable and it is obtained as major product being possible its isolation as single compound.

For compounds **1** and **2**, the *cis* isomer can exist in a low energy conformation (V) in which both, the methyl and the aromatic groups at positions 2 and 4 occupy the equatorial positions, while for the *trans* isomer in both conformers (VII and VIII) one of the substituents has to be in an axial orientation and this isomer is of higher energy. Due to the important differences of energy between the configurational isomers of compounds **1** and **2** the acetalisation reaction leads stereoselectively to the *cis* isomer.



NOTE: Ar is of higest precedence

Scheme 3

The conformational behavior of 1,3-dioxane derivatives bearing alkyl and aryl groups at position 2 was intensively investigated.[9-13] The considerably higher preference of the alkyl group for the equatorial orientation than it can be predicted by comparing the A-values of the two substituents was revealed and the shifting of the conformational equilibrium of 2-alkyl,2-aryl-1,3-dioxanes toward the conformer exhibiting the aromatic substituent in axial orientation was noticed.

For compounds **3**-**7** the *trans* isomer exhibits a conformation (XII) in which the disposition of the substituents is favorable (axial aromatic group at position 2 and equatorial methyl group at position 4), while the conformers of *cis* isomer are of higher energy. Isomers *trans* of compounds **3**-**7** are obtained stereoselectively, the acetalisation reaction undergoing under thermodynamic control.

Compounds **1**-**7** exhibit anancomeric structures the conformational equilibria being shifted towards conformer V (**1** and **2**) or conformer XII (**3**-**7**).

The anancomeric behavior of the compounds determines the recording in the NMR spectra of different signals for the axial and equatorial protons of the 1,3-dioxane ring (Table 2).

Table 2.

NMR data ($CDCl_3$; δ, ppm) for compounds **1**-**7**

Compound	position 6			position 4	
	H-eq	H-ax	$\Delta\delta_{eq-ax}$	H	CH_3
1	3.92	3.48	0.42	3.48	1.10
2	3.99	3.55	0.44	3.56	1.15
3	3.65	3.54	0.09	3.56	1.08
4	3.53	3.17	0.36	3.22	1.03
5	3.53	3.25	0.28	3.32	1.04
6	3.53	3.60	-0.07	3.62	1.14
7	3.65	3.55	0.10	3.58	1.03

As an example the spectrum of compound **5** (Figure 1) exhibit for the axial and equatorial protons at position 6 two different doublet of doublet of doublets a more deshilelded one belonging to the equatorial proton (δ = 3.53 ppm) and another one (δ = 3.25 ppm) overlapped into a doublet of triplets (the geminal and the vicinal axial-axial coupling constants exhibit close values, $^2J_{a\text{-}e} \approx {}^3J_{a\text{-}a}$) pertaining to the axial proton. The axial proton at position 4 exhibit a deshielded doublet of sextets (δ = 3.32 ppm; overlapped doublet of doublet of sextets, in which a coupling constant is two times larger than another one; $^3J_{a\text{-}a} \approx 2x^3J_{H(4)\text{-}Me}$).

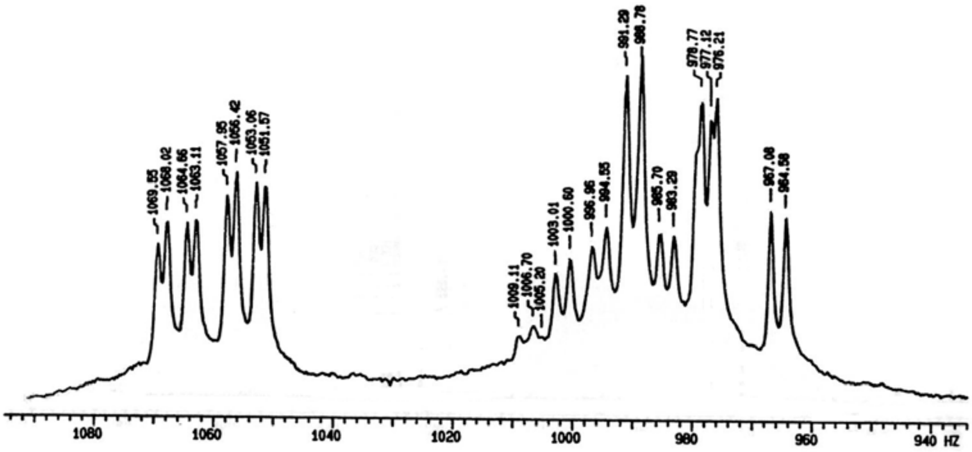


Figure 1. ^{1}H NMR spectrum (fragment) of compound 5.

CONCLUSIONS

The synthesis of 1,3-dioxane derivatives of 1,3-butanediol with aromatic aldehydes leads to *cis* isomers of 2,4-substituted 1,3-dioxane derivatives, while the reaction with alkyl, aryl ketones leads stereoselectively to the isomer exhibiting the reference groups in “*trans*” configuration. The NMR spectra reveal the anancomeric behavior of all investigated compounds and the equatorial preference of the methyl group at position 4.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded at *rt*, using $CDCl_3$ as solvent in 5 mm tubes, on a Varian Gemini) Fourier transform NMR spectrometer, equipped with a multinuclear head, operating at 300 MHz for protons and 75 MHz for carbon atoms.

M.ps were measured with Kleinfeld Apotec melting point apparatus and are uncorrected.

2-Phenyl-4-methyl-1,3-dioxane **1**

Liquid, b.p.=79 ℃ (1 mmHg), Yield 75 %. $C_{11}H_{14}O_2$, M=178.23. Found: C, 74.48; H, 8.08; required C, 74.13; H, 7.92. ^{1}H-NMR (C_6D_6) δ 0.84[1H, dddd, $^{3}J=^{3}J'=2.5$ Hz; $^{2}J=12.8$ Hz; $^{2}J=1.4$ Hz , 5-H$_{eq}$], 1.10[3H, d, $^{3}J=6.2$ Hz, 4-CH$_3$ (eq)], 1.52[1H dddd, $^{3}J=^{3}J'=12.5$ Hz; $^{2}J=12.8$ Hz; $^{3}J=5$ Hz , 5-H$_{ax}$], 3.48[1H, sd* (overlapped ddq), $^{3}J=^{3}J'=12.5$ Hz; $^{3}J=6.2$ Hz , 4-H$_{ax}$; 1H, ddd, $^{2}J=11.4$ Hz; $^{3}J=12.5$ Hz , $^{3}J=2.5$ Hz 6-H$_{ax}$], 3.92[1H, ddd, $^{2}J=11.4$ Hz; $^{3}J=5$ Hz; $^{3}J=1.4$ Hz 6-H$_{eq]}$, 5.38[1H, s, 2-H$_{ax}$], 7.20-7.50 [3H aromatic, m, overlapped peaks], 7.70-7.80[2H aromatic, m, overlapped peaks].

^{13}C-NMR (C_6D_6) δ 21.9[4-CH$_3$ (eq)], 33.1(C^5), 66.9(C^6), 73.2(C^4), 101.3(C^2) 126.7, 128.2, 128.56,140.0 (aromatic carbon atoms).

4-Methyl-2-(β-nafthyl)-1,3-dioxane **2**

Solid, white crystals, m.p.=80-81℃, Yield 58%. $C_{15}H_{16}O_2$, M= 228.29. Found C, 79.16; H, 7.28; required C, 78.92; H, 7.06. ^{1}H-NMR (C_6D_6) δ 0.89 [1H, dddd, $^{3}J=^{3}J'=2.4$Hz; $^{2}J=12.8$ Hz; $^{3}J=1.4$ Hz , 5-H$_{eq}$], 1.15[3H, d, $^{3}J=6.2$ Hz, 4-CH$_3$ (eq)], 1.58[1H dddd, $^{3}J=^{3}J'=12.4$ Hz; $^{2}J=12.8$ Hz; $^{3}J=5$ Hz , 5-H$_{ax}$], 3.55 [1H, ddd, $^{3}J=12.6$ Hz; $^{3}J=6.2$ Hz; $^{3}J=2.5$ Hz , 6-H$_{ax}$], 3.56[1H, ddq, $^{2}J=11.3$ Hz; $^{3}J=12.4$ Hz , $^{3}J=2.5$ Hz 4-H$_{ax}$], 3.99[1H, ddd, $^{2}J=11.4$ Hz; $^{3}J=5$ Hz; $^{3}J=1.4$ Hz 6-H$_{eq}$], 5.52[1H, s, 2-H$_{ax}$] 7.10-7.30[2H aromatic,m, overlapped peaks], 7.60-7.70[5H aromatic, m, overlapped peaks], 7.87[1H aromatic, d, $^{3}J=8.0$ Hz], 8.15[1H aromatic, s, α-H]. ^{13}C-NMR (C_6D_6) δ 22.0[4-CH$_3$ (eq)], 33.2(C^5), 67.0(C^6), 73.3(C^4), 101.6(C^2), 124.9, 126.0, 126.3, 127.5, 127.7, 128.1128.4, 128.7, 133.6, 134.0, 137.4(aromatic carbon atoms).

2-Phenyl-2,4-dimethyl-1,3-dioxane **3**

Solid, white crystals, m.p.=52-53 ℃, Yield 68%. $C_{12}H_{16}O_2$, M= 192.26. Found C, 74.85; H, 8.21; required C, 74.97; H, 8.39. ^{1}H-NMR (C_6D_6) δ 0.73[1H, dddd, $^{3}J=^{3}J'=2.5$Hz; $^{2}J=12.6$ Hz; $^{3}J=1.5$ Hz , 5-H$_{eq}$], 1.08[3H, d, $^{3}J=6.2$ Hz, 4-CH$_3$ (eq)], 1.53[1H dddd, $^{3}J=^{3}J'=12.4$ Hz; $^{2}J=12.6$ Hz; $^{3}J=5.2$ Hz , 5-H$_{ax}$], 1.6[3H, s, 2-CH$_3$ (eq)], 3.54 [1H, ddd, $^{3}J=12.4$ Hz; $^{3}J=6.2$ Hz; $^{3}J=2.5$ Hz , 6-H$_{ax}$], 3.54[1H, ddq, $^{2}J=11.4$ Hz; $^{3}J=12.4$ Hz , $^{3}J=2.5$ Hz 4-H$_{ax}$], 3.65[1H, ddd, $^{2}J=11.4$ Hz; $^{3}J=5.2$ Hz; $^{3}J=1.5$ Hz 6-H$_{eq}$], 7.10-7.35 [3H aromatic, m, overlapped peaks], 7.50-7.70[2H aromatic, m, overlapped peaks],.

^{13}C-NMR (C_6D_6) δ 22.1[2-CH$_3$ (eq)], 33.0[4-CH$_3$ (eq)], 33.38(C^5), 61.2(C^4), 66.5(C^6), 101.1(C^2) 127.1; 127.6; 128.0; 128.3; 128.9, 142.7 (aromatic carbon atoms).

2,4-dimethyl-2-(p-nitrophenyl)-1,3-dioxane **4**

Solid, white crystals, m.p.=103-104 ℃, Yield 64%. $C_{12}H_{15}NO_4$, M= 237.26. Found C, 60.98; H, 6.15; N, 5.71 required C, 60.75; H, 6.37; N 5.90. ^{1}H-NMR (C_6D_6) δ 0.71[1H, dddd, $^{3}J=^{3}J'=2.45$Hz; $^{2}J=11.6$ Hz; $^{3}J=1.5$ Hz, 5-H$_{eq}$], 1.03[3H, d, $^{3}J=6.1$ Hz, 4-CH$_3$ (eq)], 1.46[1H dddd, $^{3}J=^{3}J'=12.4$ Hz; $^{2}J=12.9$ Hz; $^{3}J=5.0$ Hz,

5-H$_{ax}$], 1.48[3H, s, 2-CH$_3$ (eq)] 3.17 [1H, ddd, ^{3}J=12.4 Hz; ^{2}J=11.6 Hz; ^{3}J=2.45 Hz, 6-H$_{ax}$], 3.22[1H, ddq, ^{3}J=12.4 Hz , ^{3}J=6.1 Hz;^{3}J=2.45 Hz 4-H$_{ax}$], 3.53[1H, ddd, ^{2}J=11.6 Hz; ^{3}J=5.0 Hz; ^{3}J=1.5 Hz 6-H$_{eq}$], 7.13[2H, aromatic, d, ^{3}J=2.83 Hz], 7.85[2H, aromatic, d, ^{3}J=2.83 Hz].
^{13}C-NMR (C_6D_6) δ 21.9[2-CH$_3$ (eq)], 32.6[4-CH$_3$ (eq)], 32.7(C^5), 61.4(C^4), 67.0(C^6), 100.4(C^2) 124.0, 127.8, 128.3, 147.6(aromatic carbon atoms).

2,4-dimethyl-2-(o-nitrophenyl)-1,3-dioxane **5**

Solid, white crystals, m.p.=102-103 ℃, Yield 65%. $C_{12}H_{15}NO_4$, M= 237.26. Found C, 60.58; H, 6.11; N, 5.66 ; required C, 60.75; H, 6.37; N, 5.9. ^{1}H-NMR (C_6D_6) δ 0.57[1H, dddd, ^{3}J=^{3}J'=2.5Hz; ^{2}J=12.8 Hz; ^{3}J=1.6 Hz , 5-H$_{eq}$], 1.04[3H, d, ^{3}J=6.1 Hz, 4-CH$_3$ (eq)], 1.36[1H dddd, ^{3}J=^{3}J'=12.5 Hz; ^{2}J=12.8 Hz; ^{3}J=5.2 Hz , 5-H$_{ax}$], 1.9[3H, s, 2-CH$_3$ (eq)] 3.25 [1H, ddd, ^{3}J=12.5 Hz; ^{2}J=11.5 Hz; ^{3}J=2.5 Hz , 6-H$_{ax}$], 3.32[1H, ddq, ^{3}J=12.5 Hz , ^{3}J=6.1 Hz;^{3}J=2.5 Hz 4-H$_{ax}$], 3.53[1H, ddd, ^{2}J=11.5 Hz; ^{3}J=4.9 Hz; ^{3}J=1.5 Hz 6-H$_{eq}$], 6.50-7.50[4H aromatic, m, overlapped peaks].^{13}C-NMR (C_6D_6) δ 21.6 [2-CH$_3$ (eq)], 31.8 [4-CH$_3$ (eq)], 32.2 (C^5), 61.8 (C^4), 67.9 (C^6), 123.4 (C^2) 127.7, 128.0, 128.3, 128.9, 129.5, 130.5 (aromatic carbon atoms).

2,4-Dimethyl-2-(α-nafthyl)-1,3-dioxane **6**

Solid, white crystals, m.p.=54-56 ℃, Yield 57%. $C_{16}H_{18}O_2$, M= 242.32. Found C, 79.03; H, 7.71; required C, 79.31; H, 7.49. ^{1}H-NMR (C_6D_6) δ 0.77[1H, dddd, ^{3}J=^{3}J'=2.5Hz; ^{2}J=12.6 Hz; ^{3}J=1.5 Hz , 5-H$_{eq}$], 1.14[3H, d, ^{3}J=6.2 Hz, 4-CH$_3$ (eq)], 1.58[1H dddd, ^{3}J=^{3}J'=12.4 Hz; ^{2}J=12.6 Hz; ^{3}J=5.2 Hz , 5-H$_{ax}$], 1.79(3H, s, 2-CH$_3$), 3.60 [1H, ddd, ^{3}J=12.4 Hz; ^{2}J=11.4 Hz; ^{3}J=2.5 Hz , 6-H$_{ax}$], 3.62[1H, ddq, ^{3}J=12.4 Hz , ^{3}J=6.2 Hz;^{3}J=2.5 Hz 4-H$_{ax}$], 3.53[1H, ddd, ^{2}J=11.4 Hz; ^{3}J=2.5 Hz; ^{3}J=1.5 Hz 6-H$_{eq}$], 7.20-7.80[7H aromatic, m, overlapped peaks]. ^{13}C-NMR (C_6D_6) δ 22.22[2-CH$_3$ (eq)], 33.09[4-CH$_3$ (eq)], 33.38(C^5), 61.40(C^4), 66.73(C^6), 101.37(C^2), 124.4, 125.1, 126.3, 126.7, 127.7, 128.4, 129.0, 130.3, 133.4, 140.3.(aromatic carbon atoms).

2-ethyl-2-phenyl-4-methyl-1,3-dioxane **7**

Liquid, b.p.=64-68 ℃ (1 mmHg), Yield 71%. $C_{13}H_{18}O_2$, M=206.29. Found: C, 75.90; H, 9.02; required C, 75.69; H, 8.79. ^{1}H-NMR (C_6D_6) δ 0.73[1H, dddd, ^{3}J=2.5 Hz; ^{2}J=12.6 Hz; ^{3}J=1.4 Hz , 5-H$_{eq}$], 1.03[3H, t, overlapped peaks ^{3}J=7.2 Hz(cis), ^{3}J=7.45 Hz(trans) 2-$\underline{CH_3}$-CH$_2$-(cis, trans)], 1.08[3H, d, ^{3}J=6.2 Hz, 4-CH$_3$ (eq)], 1.97[2H, q, ^{3}J=7.45 Hz; 2-CH$_3$-$\underline{CH_2}$-(trans)], 2.43 [2H, q, ^{3}J=7.2 Hz; 2-CH$_3$-$\underline{CH_2}$-(cis)], 1.51[1H dddd, ^{3}J=^{3}J'=12.4 Hz; ^{2}J=12.6 Hz; ^{3}J=5.2 Hz , 5-H$_{ax}$], 3.55[1H, ddd ^{3}J=12.4 Hz; ^{2}J=11.3 Hz; ^{3}J=2.5 Hz 6-H$_{ax}$], 3.58[1H, ddq, ^{3}J=12.4 Hz; ^{3}J=6.2 Hz; ^{3}J=2.5 Hz 4-H$_{ax}$], 3.65[1H, ddd, ^{2}J=11.3 Hz; ^{3}J=2.5 Hz; ^{3}J=1.6 Hz 6-H$_{eq}$], 7.15-7.30 [3H aromatic, m, overlapped peaks], 7.45-7.55[2H aromatic, m, overlapped peaks].^{13}C-NMR (C_6D_6) δ 7.73[2-CH$_3$ (ax)], 22.10[2-CH$_3$ (eq)], 33.25[4-CH$_3$ (eq)], 38.49(C^5), 61.15(C^4), 66.36(C^6), 102.64(C^2) 127.7, 128.1, 128.6, 132.5, 141.3. (aromatic carbon atoms).

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