SYNTHESIS AND STEREOCHEMISTRY OF SOME NEW 1,3-DIOXANE DERIVATIVES OF *o*-PHTHALDIALDEHYDE

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Abstract: The stereochemistry of some acetals of o-phthaldialdehyde with 2-substituted-1,3-propanediols have been investigated by NMR methods. The *trans, trans* , *cis, cis* and *cis, trans* diastereoisomers of some of these compounds have been observed by the NMR spectra using the specific values of the coupling constants and NOE experiments.

INTRODUCTION

The studies[1-4] on the stereochemistry of some 2-aryl-1,3-dioxanes revealed the high conformational free enthalpy of the aromatic groups (*e.g.*. ΔG^{o}_{Ph}=3.12 kcal/mol)[2] and the efficient use of this type of substituents as "holding group".

The studies[5] on the stereochemistry of some 1,3-dioxane derivatives of o-phthaldialdehyde showed the equatorial orientation of the aromatic ring with respect to both heterocycles. The corresponding *cis* and *trans* diastereoisomers of the compounds bearing a carboxy or an ester group in the positions 5 and 5' (aliphatic part of the rings) have been identified (NMR spectra and TLC) and separated (preparative TLC).

It was considered of interest to study the stereochemistry of some new 1,3-dioxane compounds obtained from o-phthaldialdehyde and to identify the diastereoisomers of these derivatives generated by the axial or equatorial orientations of the substituents located in the position 5 of the 1,3-dioxane ring.

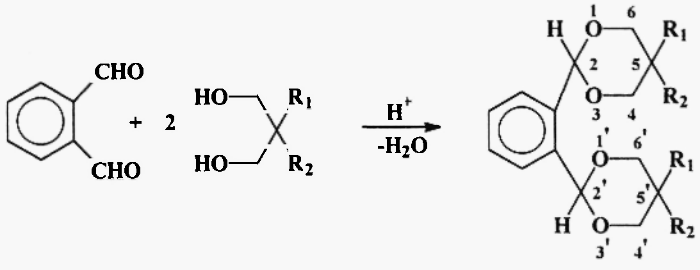
RESULTS AND DISCUSSION

New compounds displaying two 1,3-dioxane rings have been obtained by the acetalization reaction of o-phthaldialdehyde with some 2-substituted-1,3-propanediols (Scheme 1).

All the investigated compounds exhibit anancomeric structures showing equatorial orientations for the phenylene group in both heterocycles. The NMR spectra of the compounds display different signals for the axial and equatorial protons of the rings and in the case of compound **2** for the protons and carbon atoms of the similar groups located in the positions 5 and 5' of the heterocycles (^{1}H NMR: $\delta_{Me(ax)}$=1.25, $\delta_{Me(eq)}$=0.39; ^{13}C NMR: $\delta_{Me(ax)}$=23.32, $\delta_{Me(eq)}$=21.73 ppm). The higher deshielding of the protons and carbon atoms of the axial methyl group, in agreement with the data reported for other anancomeric 5,5-dimethyl-1,3-dioxane,[1,6-9] is due to the influence (through space) of the oxygen atoms of the heterocycles.

The ^{1}H NMR spectrum of compound **2** shows for the protons of the positions 4(4') and 6(6') an AX splitting pattern the differences of the chemical shifts between the equatorial and axial protons (Table 1) being in the usual range.[1,6-9]

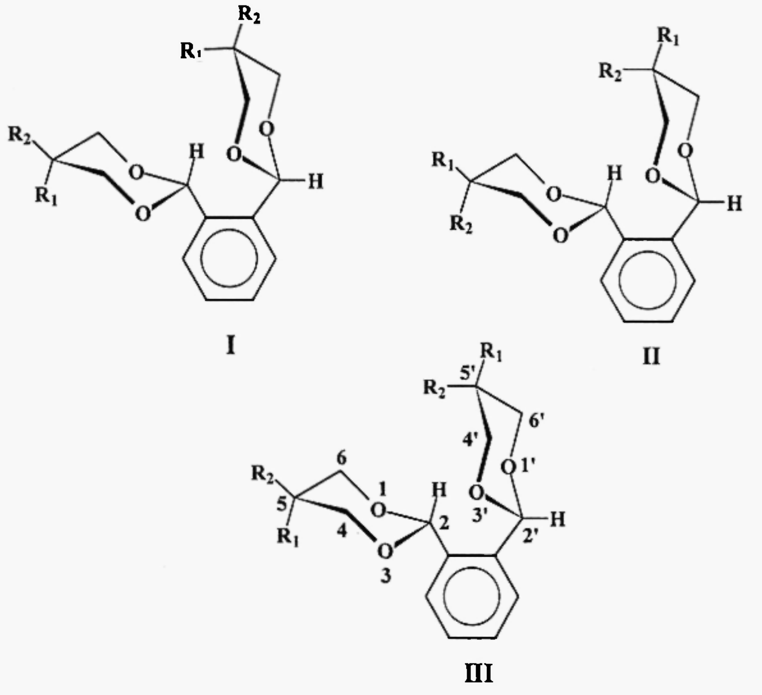
Compounds **3-5** can exhibit three diastereoisomers (Scheme 2) correlated to the *cis* or *trans* disposition of the substituents located in the position 5 (5') and of the phenylene group of the position 2 (2').



R_1=R_2=H	**1**
R_1=R_2=CH_3	**2**
R_1=H, R_2=CH_3	**3**
R_1=H, R_2=C_6H_5	**4**
R_1=CH_3, R_2=C_2H_5	**5**

Scheme 1

Let us consider as I the diastereoisomer that exhibits in both rings the reference groups (R_2) of positions 5 or 5' (methyl for compound **3**, phenyl for compound **4** and ethyl for compound **5**) and the phenylene group of positions 2 (2') in *trans;* as II, the diastereoisomer showing the mentioned groups in *cis* with respect to both heterocycles and as III, the third isomer, that displays these groups in *cis* with respect to one of the rings and in *trans* with respect to the second one.



Scheme 2

In the synthesis of compounds **3** and **4** (showing only one substituent in the aliphatic part of the 1,3-dioxane rings) only the diastereoisomer I is obtained in significant amount (NMR and TLC investigations). This diastereoisomer exhibits in both rings all the substituents in equatorial orientations.

The ^{1}H NMR spectrum of compound **3** (Figure 1, Table 1) shows only one set of signals corresponding to the two equivalent heterocycles. The axial orientation of the protons of positions 5 and 5' have been determined from the values of their coupling constants with the equatorial and axial protons located in the positions 4 (4') and 6 (6'). Thus, the equatorial protons belonging to the positions 4 (4') and 6 (6') exhibit a deshielded [$\delta_{4(4'),6(6')eq}$=4.02 ppm] doublet of doublets showing a large geminal coupling constant with the axial protons [$J_{4(6)eq-4(6)ax}$=10.9 Hz] and a smaller vicinal coupling constant [$J_{4(6)eq-5(ax)}$=4.7 Hz] with the axial protons of positions 5 (5'). The axial protons exhibit an overlapped doublet of doublets [giving a triplet, $\delta_{4(4'),6(6')ax}$=3.29 ppm] displaying two large coupling constant with very close values [$J_{4(6)eq-4(6)ax}=J_{4(6)ax-5(ax)}$=10.9 Hz] corresponding to the couplings of these protons with the geminal equatorial protons and with the axial protons of positions 5 (5'). The values of the coupling constants of the proton of positions 5 (5') with the protons of positions 4 (4') and 6 (6') are in the normal range for coupling constants between vicinal axial-equatorial and axial-axial protons located in the 1,3-dioxane ring.[10]

Table 1. ^{1}H NMR data (δ ppm) of the 1,3-dioxane rings in compounds **1-5**.

Compound	positions 2 (2')	positions 4 (4'), 6 (6')		
		equatorial	axial	Δ
1	5.96	3.95	3.58	0.37
2	5.94	3.60	3.42	0.18
3 (diastereoisomer I)	6.00	4.02	3.29	0.73
4 (diastereoisomer I)	6.18	4.25	3.87	0.38
5 (cycles A)	(5.989, 5.992	3.82	3.435, 3.439	0.38
5 (cycles B)	6.002, 6.005)	3.73	3.50	0.23

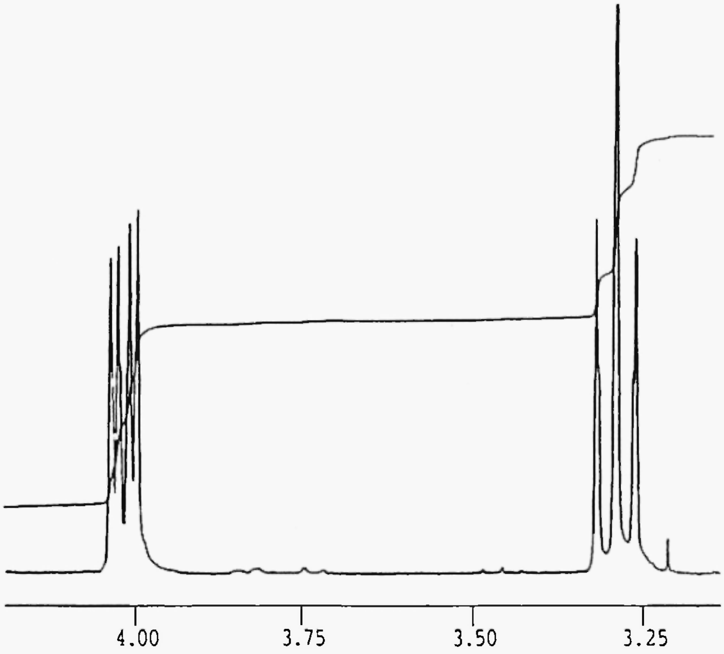


Figure 1. ^{1}H NMR spectrum of compound **3** [fragment corresponding to the protons of the positions 4 (4') and 6 (6')].

The insignificant differences of conformational free enthalpies between the methyl and ethyl groups located in the aliphatic part of the 1,3-dioxane ring (ΔG^{o}_{Me}=0.80-0.89 and ΔG^{o}_{Et}=0.75-0.81 kcal/mol)[1] results in the formation in the synthesis of compound **5** of a mixture of all possible diastereoisomers in a ratio imposed by statistic rules (I:II:III=1:1:2). The ^{1}H NMR spectrum of this compound (mixture of diastereoisomers) shows for the protons of the positions 2 and 2' four signals with close intensities (Figure 2a). The protons of the positions 2 and 2' are equivalent in isomer I, as well as in isomer II, but they are different in isomer III. The recording for the acetalic protons of four signals with close intensities could be explained taking also into account that the diastereoisomer III has been obtained in a ratio two times larger than the diastereoisomers I or II. On the other hand the signals of these three diastereoisomers are not completely separated and the NMR characterisation of these isomers was not possible. The ^{1}H NMR spectrum shows two main sets of signals, with close intensities, one of them belonging to the 1,3-dioxane rings bearing equatorial ethyl substituents (rings A) in the position 5 (or 5') and another one pertaining to the heterocycles exhibiting axial ethyl groups (rings B) located in the positions 5 (or 5'). The signals belonging to the axial or equatorial methyl and ethyl groups of the positions 5 and 5' could be identified taking into account the considerably higher deshielding of the axial groups [for the ethyl groups: $\Delta\delta(CH_2)_{ax-eq}\approx1.0$ ppm and $\Delta\delta(CH_3)_{ax-eq}\sim0.25$ ppm and for the methyl groups $\Delta\delta_{ax-eq}\approx0.9$ ppm]. The assignment of the signals (Figure 2b, Table 1) belonging to the two different substituted heterocycles (rings A and B) has been made using NOE experiments. The irradiation of the singlet belonging to the axial methyl groups (δ=1.28 ppm) shows in the NOEDiff. spectrum a high influence on the signal (δ=3.82 ppm) belonging to the equatorial protons of the rings A (exhibiting axial methyl groups) and the irradiation of the signal (δ=1.85 ppm) of the methylene protons of the axial ethyl groups shows an influence on the signal (δ=3.73 ppm) of the equatorial protons of the rings B (exhibiting axial ethyl groups) The irradiation of the signals pertaining to the equatorial methyl groups (δ=0.371, 0.376 ppm) determines the recording in the NOEDiff. spectrum of an influence on both signal belonging to the axial and equatorial protons of ring B (higher influence on the signal of the axial ones, δ=3.50 ppm). For the equatorial substituents belonging to different diastereoisomers (5-Me, isomers II and III; 5-Et, isomers I and III) different signals with close chemical shifts have been recorded.

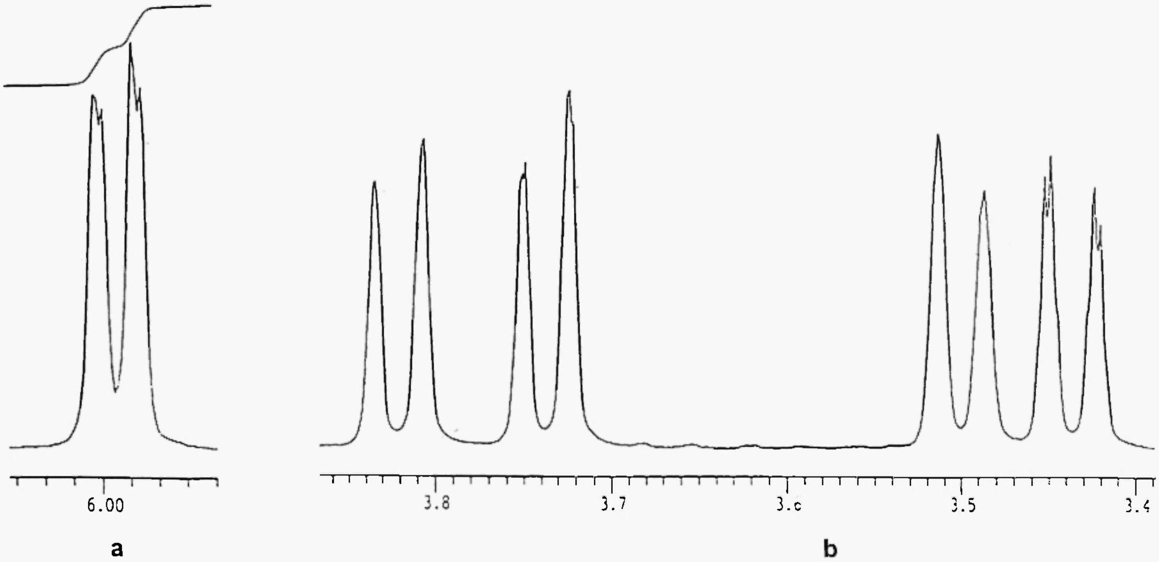


Figure 2. ^{1}H NMR spectrum (fragments) of compound **5** [a: signals belonging to the protons of the positions 2 (2'); b: signals corresponding to the protons of the positions 4 (4') and 6 (6')].

The COSY LR spectra of compounds **2** and **5** showed the long-range coupling between the axial protons of the heterocycles (positions 4 (4') and 6 (6') and the protons of the axial groups located in the position 5 (Me or Et) due to the W arrangement of the bonds H_{ax}-$C^{4(6)}$-C^{5}-$C^{\alpha}{}_{ax}$-H. Using the J-resolved spectra the values of these coupling constants have been measured (compound **2**: ^{4}J=1.15 Hz and compound **5**: ^{4}J=1.0 Hz). The assignment of the signals in the ^{13}C NMR spectra for the axial and equatorial groups of of these compounds has been made on the basis of the results of 2D HETCOR spectra.

CONCLUSIONS

The 1,3-dioxane acetals of o-phthaldialdehyde exhibit anancomeric structures. The *o*-phenylene group shows an equatorial orientation with respect to both heterocycles. Despite the lower conformational energies of the substituents located in the positions 5 of the 1,3-dioxane ring than in the position 2 of the heterocycle, the synthesis of compounds **3** and 4 lead only to the diastereoisomers displaying all the substituents in equatorial positions. In the synthesis of compound **5** all the possible diastereoisomers (*cis* and *trans*) have been obtained in agreement with the very close conformational free enthalpies of the substituents located in the aliphatic part of the heterocycles.

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 (Varian Gemini)* Fourier transform NMR spectrometer, equipped with a dual ^{13}C-^{1}H head, operating at 400 (300)* MHz for protons and 100 (75)* MHz for carbon atoms.

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

Compounds 1-5, general procedure. - Stoichiometric amounts of 1,3-diol (0.2 mol) and o-phthaldialdehyde (0.1 mol) with catalytic amounts of p-toluenesulphonic acid (0.1 g) were solved in 200 ml benzene. The mixture was refluxed and the water resulted in the reaction was removed using a Dean-Stark trap. When 80 % of the theoretical water was separated, after cooling at room temperature, the catalyst was neutralised (under stirring 0.5 h) with CH_3-COONa powder in excess (0.2 g). The reaction mixture was washed twice with 100 ml water. After drying (with Na_2SO_4) the benzene was removed and the 1,3-dioxane compounds were purified by crystallisation from ethanol (compounds **2-5**) or heptane (compound **1**).

1,2-Bis(1,3-dioxane-2-yl)-benzene 1. Solid, m.p.=110-111 °C. Yield 73%. Anal. Calcd. for $C_{14}H_{18}O_4$; C, 67.18, H, 7.25. Found: C, 67.32, H, 7.40. ^{1}H NMR δ (C_6D_6) 0.71[2H, dt, J=12.5 Hz, J'=2.5Hz, 5(5')-H_{eq}], 1.94[2H, ddt, J=J'=12.5 Hz, J"=5.2 Hz 5(5')-H_{ax}], 3.58[4H, dt, J=12.5, J'=2.5 Hz, 4(4')-H_{ax}, 6(6')-H_{ax}], 3.95[4H, dd, J=12.5 Hz, J'=5.2 Hz, 4(4')-H_{eq}, 6(6')-H_{eq}], 5.96[2H, s, 2(2')-H_{ax}], 7.18(2H, m, aromatic protons) and 8.18 ppm (2H, m, aromatic protons). ^{13}C NMR δ (C_6D_6) 26.14($C^{5,5'}$), 67.41($C^{4,4'\,6,6'}$), 99.90($C^{2,2'}$), 126.48, 128.39(tertiary aromatic carbon atoms) and 136.60 ppm (quaternary aromatic carbon atom).

1,2-Bis(5,5-dimethyl-1,3-dioxane-2-yl)-benzene 2. Solid, m.p.=108-109 °C. Yield 77%. Anal. Calcd. for $C_{18}H_{26}O_4$; C, 70.56, H, 8.55. Found: C, 70.71, H, 8.69. ^{1}H NMR δ (C_6D_6) 0.39[6H, s, 5(5')-CH_3(eq)], 1.25[6H, s, 5(5')-CH_3(ax)], 3.42[4H, d, J=10.9 Hz, 4(4')-H_{ax}, 6(6')-H_{ax}], 3.60[4H, d, J=10.9 Hz, 4(4')-H_{eq}, 6(6')-H_{eq}], 5.94[2H, s, 2(2')-H_{ax}], 7.18(2H, m, aromatic protons) and 8.10 ppm (2H, m, aromatic protons). ^{13}C NMR δ (C_6D_6) 21.73[5(5')-CH_3(eq)], 23.32[5(5')-CH_3(ax)], 30.11($C^{5,5}$), 77.84($C^{4,4',6,6}$), 99.98($C^{2,2'}$), 126.55, 128.77(tertiary aromatic carbon atoms) and 136.71 ppm (quaternary aromatic carbon atom).

1,2-Bis(5-methyl-1,3-dioxane-2-yl)-benzene 3. Solid, m.p.=117-118 °C. Yield 70%. Anal. Calcd. for $C_{16}H_{22}O_4$; C, 69.04, H, 7.97. Found: C, 69.23, H, 7.84. ^{1}H NMR δ (C_6D_6) 0.31[6H, d, J=6.8 Hz, 5(5')-CH_3(eq)], 2.06(2H, m, 5(5')-H_{ax}), 3.29[4H, t(overlapped dd), J=J'=10.9 Hz, 4(4')-H_{ax}, 6(6')-H_{ax}], 4.02[4H, dd, J=10.9 Hz, J'=4.7 Hz, 4(4')-H_{eq}, 6(6')-H_{eq}], 6.00[2H, s, 2(2')-H_{ax}], 7.22(2H, m, aromatic protons) and 8.13 ppm (2H, m, aromatic protons). ^{13}C NMR δ (C_6D_6) 11.83[5(5')-CH_3(eq)], 29.22($C^{5,5}$), 73.48($C^{4,4,6,6}$), 99.31($C^{2,2}$), 126.18, 128.32(tertiary aromatic carbon atoms) and 136.44 ppm (quaternary aromatic carbon atom).

1,2-Bis(5-phenyl-1,3-dioxane-2-yl)-benzene 4. Solid, m.p.=197-198 °C. Yield 75%. Anal. Calcd. for $C_{26}H_{26}O_4$; C, 77.59, H, 6.51. Found: C, 77.45, H, 6.65. ^{1}H NMR δ (C_6D_6) 3.26(2H, m, 5(5')-H_{ax}), 3.87[4H, t(overlapped dd), J=J'=10.6 Hz, 4(4')-H_{ax}, 6(6')-H_{ax}], 4.25[4H, dd, J=10.6 Hz, J'=4.6 Hz, 4(4')-H_{eq}, 6(6')-H_{eq}], 6.18[2H, s, 2(2')-H_{ax}], 6.8-7.3(12H, overlapped peaks, aromatic protons) and 8.20 ppm (2H, m, aromatic protons). ^{13}C NMR δ (C_6D_6) 41.51($C^{5,5}$), 72.64($C^{4,4',6,6'}$), 99.77($C^{2,2}$), 126.56, 127.48, 128.79, 128.92(tertiary aromatic carbon atoms) and 136.41, 136.67 ppm (quaternary aromatic carbon atom).

1,2-Bis(5-ethyl-5-methyl-1,3-dioxane-2-yl)-benzene 5. Solid, m.p.=65-68 °C. Yield 80%. Anal. Calcd. for $C_{20}H_{30}O_4$; C, 71.82, H, 9.04. Found: C, 71.72, H, 9.15. ^{1}H NMR δ (C_6D_6) 0.371, 0.376[3H, s, 5(5')-CH_3(eq)], 0.601, 0.607[3H, t, J=7.1 Hz, 5(5')-CH_2-$C\underline{H}_3$(eq)], 0.829, 0.836[2H, q, J=7.1 Hz, 5(5')-$C\underline{H}_2$-CH_3(eq)], 0.85[3H, t, J=7.5Hz, 5(5')-CH_2-$C\underline{H}_3$(ax)], 1.29[3H, s, 5(5')-CH_3(ax)], 1.84[2H, q, J=7.5 Hz, 5(5')-$C\underline{H}_2$-CH_3(ax)], 3.435, 3.439[2H(rings A), d, J=11.0 Hz, 4(4')-H_{ax}, 6(6')-H_{ax}], 3.50[2H(rings B), d, J=10.8 Hz, 4(4')-H_{ax}, 6(6')-H_{ax}], 3.73[2H(rings B), d, J=10.8 Hz, 4(4')-H_{eq}, 6(6')-H_{eq}], 3.82[2H(rings A), d, J=11.0 Hz, 4(4')-H_{eq}, 6(6')-H_{eq}], 5.989, 5.992, 6.002, 6.005[2H, s, 2(2')-H_{ax}], 7.19-7.26(2H, overlapped peaks, aromatic protons) and 8.07-8.14 ppm (2H, overlapped peaks, aromatic protons). ^{13}C NMR δ (C_6D_6) 6.64[5(5')-CH_2-$\underline{C}H_3$(eq)], 7.84[5(5')-CH_2-$\underline{C}H_3$(ax)], 17.76[5(5')-CH_3(eq)], 19.49[5(5')-CH_3(ax)], 26.92[5(5')-$\underline{C}H_2$-CH_3(ax)], 28.53[5(5')-$\underline{C}H_2$-CH_3(eq)], 32.31, 32.35($C^{5,5'}$)*, 75.53, 76.76($C^{4,4',6,6'}$)*, 99.63, 99.72, 99.79($C^{2,2'}$)*, 126.17, 128.33(tertiary aromatic carbon atoms) and 136.39, 136.49 ppm (quaternary aromatic carbon atom).

*separated signals for rings A and B

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