SYNTHESIS AND STEREOCHEMISTRY OF SOME NEW 1,3-DIOXANE DERIVATIVES OBTAINED FROM 1,3-BENZENEDICARBOXALDEHYDE

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Abstract: The stereochemistry of some new 1,3-dioxane derivatives obtained by the acetalization of isophthalaldehyde with several 1,3-propanediols have been investigated by NMR methods. The anancomeric structure of the compounds, the equatorial orientation of the aromatic group in both heterocycles and the *cis* and *trans* isomerism of some of these compounds has been revealed.

INTRODUCTION

Recent studies[1-3] on the stereochemistry of 2-aryl-1,3-dioxane derivatives with two heterocycles located in the same aromatic ring revealed interesting aspects. The high A-value of the aromatic substituent[4] determines, in compounds obtained from *ortho* and *para* benzenedicarboxaldehydes, anancomeric structures exhibiting the aromatic substituent ("holding group") in equatorial orientation for both heterocycles. The compounds showing different substituents at the positions 5 and 5' of the 1,3-dioxane rings were obtained as mixtures of diastereoisomers, their identification being possible using the values of coupling constants and NOE experiments. The separation of some of these isomers by crystallization or by preparative TLC has been reported.

It has been considered of interest to investigate new derivatives obtained starting from isophthalaldehyde and to observe the influence of the proximity of the two heterocycles on the stereochemistry and NMR spectra of these compounds.

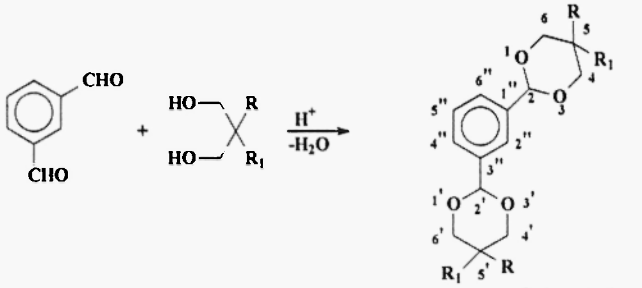
RESULTS AND DISCUSSIONS

New 1,3-dioxane derivatives have been obtained by the reaction of isophthalaldehyde with several 1,3-propanediols (Scheme 1).

All investigated compounds exhibit anancomeric structures, the characteristic conformational equilibrium for the flipping of the heterocycles (Scheme 2) being shifted toward the conformations showing the aromatic group in equatorial position for both 1,3-dioxane rings (**A** $\rightleftharpoons$ **B** $\rightleftharpoons$ **D**, **A** $\rightleftharpoons$ **C** $\rightleftharpoons$ **D**).

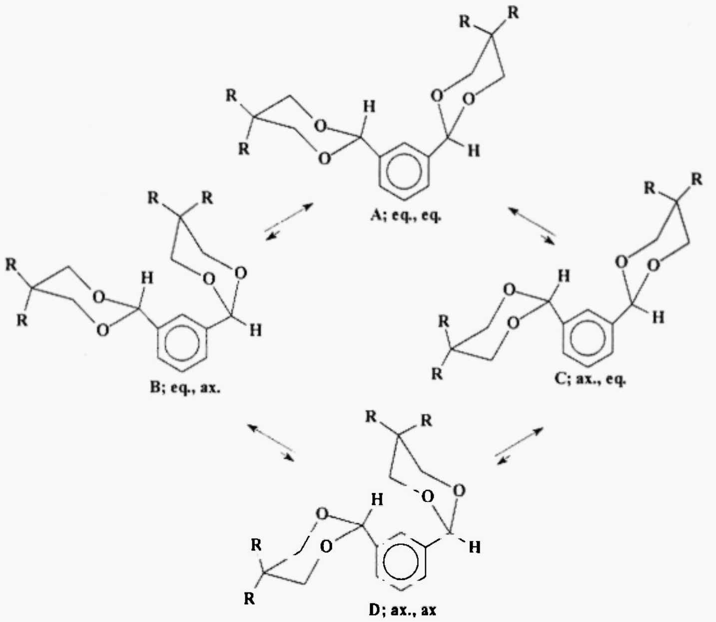
Compounds **1-3** are unique diastereoisomers, whereas compounds **4-6** can exhibit three configurational isomers in agreement with the *cis* and *trans* disposition of the aromatic group at positions 2 and 2' of the heterocycles and the group of highest precedence located at the positions 5 and 5' of the 1,3-dioxane rings (Scheme 3).

The NMR spectra of compounds **1-3** are quite simple showing unique sets of signals for the two 1,3-dioxane rings. Due to the anancomericity of the heterocycles different signals (Table 1) for the equatorial and axial protons of positions 4 and 6 (4' and 6') and for the protons and carbon atoms of the similar groups at positions 5 and 5' are recorded.

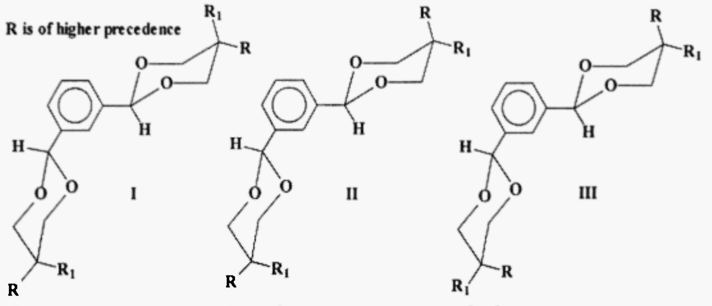


R=R$_1$=H	**1**
R=R$_1$=CH$_3$	**2**
R=R$_1$=COOC$_2$H$_5$	**3**
R=H, R$_1$=CH$_3$	**4**
R=H, R$_1$=C$_6$H$_5$	**5**
R= CH$_3$, R$_1$=C$_2$H$_5$	**6**

Scheme 1



Scheme 2



Scheme 3

Compounds 4 and **5** were obtained as mixtures of *trans-trans* (I) and *cis-trans* (II) isomers, the isomer exhibiting the substituents at position 5 (5') in equatorial orientation in both heterocycles being the major one (ratio, measured in crude products > 90 %). The spectra of the main isomer exhibit for the protons of the heterocycles [positions 4 (4') and 6 (6')] two doublets of doublets, one of them, belonging to the axial protons, is overlapped into a triplet (two large and close coupling constants; $J_{4(4\ )a,6(6')a-4(4\ )e-6(6\ )e} \approx J_{4(4')a,6(6')a-5(5')a} \approx$ 11.4 Hz, characteristic values for geminal and vicinal axial-axial protons), while the other one, is well resolved (large $J_{4(4')a,6(6')a-4(4')e-6(6')e}$ = 11.4 Hz and smaller $J_{4(4')e,6(6')e-5(5')a} \approx$ 4 Hz coupling constants, characteristic value for vicinal axial-equatorial protons).

Table 1. ^{1}H NMR data (δ, ppm, C_6D_6) for compounds **1-6**

Compound	Positions 2 (2')	positions 4 (4'), 6 (6')		
		Equatorial	axial	Δ
1[T]	5.53	3.87	3.43	0.44
2	5.28	3.52	3.26	0.26
3	5.19	5.05	3.95	1.10
4 (diastereoisomer I)	5.34	3.90	3.09	0.81
5 (diastereoisomer I)	5.46	4.15	3.69	0.46
6 (cycles A)	(5.286, 5.295	3.60	3.28	0.32
6 (cycles B)	5.311, 5.320)	3.69	3.22	0.47

[T] Spectrum run in $CDCl_3$

The insignificant difference between the A-values of a methyl (A_{Me} = 0.80-0.89 kcal/mol)[4] and an ethyl group (A_{Et} = 0.67-0.81 kcal/mol)[4] determines the obtaining in the synthesis of **6** of all three diastereoisomers in a ratio corresponding to statistic rules (*trans, trans / cis, trans = trans, cis / cis, cis* = 1 / 2 / 1). The obtaining of these isomers in the mentioned ratio is supported by the results of TLC and NMR investigations. The spectrum of the mixture exhibits for the protons at positions 2 (2') four signals with very close intensities. One signal belongs to isomer I, another one to isomer III and the other two signals pertain to isomer II (the protons at positions 2 and 2' are not equivalent; one signal belongs to the proton of the ring with axial methyl group and the other one to the proton of the ring showing the ethyl group in axial position). The differences of magnetic environments of the similar protons and carbon atoms are quite different between the rings exhibiting axial methyl groups and the rings showing axial ethyl groups, but the differences among the similar rings (with axial methyl groups or with axial ethyl groups) belonging to different isomers (I and II or III and II) are not observed. The ^{1}H NMR spectrum of **6** exhibits two sets of signals, one of them for the rings showing axial methyl groups (rings of type A) and the other one for the rings displaying axial ethyl groups (B).

The reported data in the literature concerning the rotamers of aryl groups located at the acetal part of the 1,3-dioxane ring show the light preference of the equatorial aryl group for the bisectional orientation and the free rotation of this group at *rt*.[5-8] Low temperature NMR experiments performed with compounds exhibiting disymmetric aryl groups (*e.g.* 2-furyl, 2-pyridyl[*])[9] demonstrated the free rotation of the equatorial aromatic substituent even at –90°C. The *rt* and low temperature NMR experiments on compounds **1-6** confirm the free rotation of the *meta*-phenylene group in a large range of temperatures (*rt*, -90°C).

CONCLUSIONS

The NMR investigations on the stereochemistry of new compounds exhibiting two 1,3-dioxane rings connected to a *meta*-phenylene system revealed anancomeric structures exhibiting the aromatic substituent in equatorial position for both heterocycles. The compounds showing only one substituent in the aliphatic part of the 1,3-dioxane rings (positions 5 and 5') are mainly obtained as *trans-trans* isomers exhibiting these substituents in equatorial orientation.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded at *rt*, using C_6D_6 as solvent in 5 mm tubes, on a Brucker AM 400 (Varian Gemini) Fourier transform NMR spectrometer, equipped with a dual ^{1}H-^{13}C (multinuclear) head, operating at 400 MHz (300 MHz) for protons and 100 MHz (75 MHz) for carbon atoms.
M.ps were measured with Kleinfeld Apotec melting point apparatus and are uncorrected.

General Procedure for the Synthesis of Compounds 1-6: The solution of 20 mmol of 1,3-diol, 10 mmol of 1,3-benzenedicarboxaldehyde and 0.1 g of p-toluenesulphonic acid in 50 ml of toluene was refluxed and the water resulted in

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[*] The freezing, at low temperature, of the rotation of the aromatic group should generate two diastereomers. As a consequence the NMR spectra of these compounds should exhibit two sets of signals. The similarity of spectra recorded at *rt* and at low temperature suggests the free rotation of the aromatic group even at low temperature (-90°C).

the reaction was removed using a Dean-Stark trap. When the theoretical water was separated, after cooling at room temperature, the catalyst was neutralized (under stirring) with CH_3COONa powder in excess (0.2 g). The reaction mixture was washed twice with 40 ml water. The organic layer was dried (with Na_2SO_4), then toluene was removed and the crude compounds were purified by crystallization from ethanol.

1,3-Bis(1,3-dioxan-2-yl)-benzene (1)
Solid, m.p. = 55^{0}C. Yield 48%. Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.20; H 7.20. Found: C, 67.33; H 7.41.
^{1}H-NMR δ ($CDCl_3$) 1.55[2H, m, 5 (5')-H(eq)], 2.25[2H, m, 5 (5')-H(ax)], 3.43[4H, m, 4(4'),6(6')-H(ax)], 3.87[4H, m, 4(4'), 6(6')-H(eq)], 5.53[2H, s, 2(2')-H(ax)], 7.32[1H, t (overlapped dd), J=J'=7.6 Hz, 5"-H], 7.61[2H, dd, J=7.6, J'=1.7 Hz, 4"(6")-H], 8.10[1H, t, J=1.7 Hz, 2"-H). ^{13}C-NMR δ ($CDCl_3$) 26.20$C^{5(5')}$, 64.41$C^{4(4'),6(6')}$, 100.84$C^{2(2')}$, 125.22, 126.66, 127.30[tertiary aromatic carbon atoms], 138.33[quaternary aromatic carbon atoms].
1,3-Bis(5,5-dimethyl-1,3-dioxan-2-yl)-benzene (2)
Solid, m.p.=142-143^{0}C. Yield 54%. Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.58; H 8.49. Found: C, 70.69; H 8.71. ^{1}H-NMR δ (C_6D_6) 0.34[6H, s, 5(5')-CH_3(eq)], 1.16 [6H, s, 5(5')-CH_3(ax)], 3.26[4H, d, J=10.7 Hz, 4(4'),6(6')-H(ax)], 3.52[4H, d, J=10.7 Hz, 4(4'),6(6')-H(eq)], 5.28[2H, s, 2(2')-H(ax)], 7.24[1H, t (overlapped dd), J=J'=7.7 Hz, 5"-H], 7.67[2H, dd, J=7.7, J'=1.7 Hz, 4"(6")-H], 8.13[1H, t, J=1.7 Hz, 2"-H). ^{13}C-NMR δ (C_6D_6) 21.31[5(5')-CH_3(eq)], 22.80[5(5')-CH_3(ax)], 29.66$C^{5(5')}$, 77.09$C^{4(4'),6(6')}$, 101.33$C^{2(2')}$, 124.66, 126.48, 127.94 [tertiary aromatic carbon atoms], 139.14[quaternary aromatic carbon atom].
1,3-Bis(5,5-diethyloxycarbonyl-1,3-dioxan-2-yl)-benzene (3)
Solid, m.p.= 68^{0}C. Yield 63%. Anal. Calcd. for $C_{26}H_{34}O_{12}$: C, 57.99; H 6.31. Found: C, 57.83; H 6.19. ^{1}H-NMR δ (C_6D_6) 0.79[6H, t, J=7.1 Hz, 5(5')-$COOCH_2C\underline{H}_3$(eq)], 0.91[6H, t, J=7.1 Hz, 5(5')-$COOCH_2C\underline{H}_3$(ax)], 3.78[4H, q, J=7.1 Hz, 5(5')-$COOC\underline{H}_2CH_3$(eq)], 3.95[4H, d, J=10.2 Hz, 4(4'),6(6')-H(ax)], 4.02[4H, q, J=7.1 Hz, 5(5')-$COOC\underline{H}_2CH_3$(ax)], 5.05[4H, d, J=10.2 Hz, 4(4'),6(6')-H(eq)], 5.19[2H, s, 2(2')-H(ax)], 7.12[1H, t (overlapped dd), J=J'=7.7 Hz, 5"-H], 7.55[2H, dd, J=7.7, J'=1.7 Hz, 4"(6")-H], 7.91[1H, t, J=1.7 Hz, 2"-H). ^{13}C-NMR δ (C_6D_6) 13.83[5(5')-$COOCH_2\underline{C}H_3$(eq)], 13.91[5(5')-$COOCH_2\underline{C}H_3$(ax)], 53.71$C^{5(5')}$, 61.70[5(5')-$COOCH_2CH_3$(eq)], 61.92[5(5')-$COOCH_2CH_3$(ax)], 69.84$C^{4(4'),6(6')}$, 101.56$C^{2(2')}$, 125.08, 127.09, 128.38[tertiary and quaternary aromatic carbon atoms], 138.35[quaternary aromatic carbon atom], 167.06[5(5')-$\underline{C}OOCH_2CH_3$(eq)], 167.86[5(5')-$COOCH_2CH_3$(ax)].
1,3-Bis(5-methyl-1,3-dioxan-2-yl)-benzene (4)
Solid, m.p.=80-1^{0}C. Yield 59%. Anal. Calcd. for $C_{16}H_{22}O_4$: C, 69.06; H 7.91. Found: C, 69.31; H 7.67. ^{1}H-NMR δ (C_6D_6) 0.21[6H, d, J=6.7 Hz, 5(5')-$C\underline{H}_3$(eq)], 1.93[2H, m, 5(5')-H(ax)], 3.09[4H, overlapped dd, J~J'=11.4 Hz, 4(4'),6(6')-H(ax)], 3.90[4H, dd, J=11.6 Hz, J'=4.6 Hz, 4(4'),6(6')-H(eq)], 5.34[2H, s, 2(2')-H(ax)], 7.23[1H, t (overlapped dd), J=J'=7.6 Hz, 5"-H], 7.68[2H, dd, J=7.6, J'=1.7 Hz, 4"(6")-H], 8.16[1H, t, J=1.7 Hz, 2"-H). ^{13}C-NMR δ (C_6D_6) 11.76[5(5')-CH_3(eq)], 29.10 $C^{5(5')}$, 73.12$C^{4(4'),6(6')}$, 100.98$C^{2(2')}$, 124.79, 126.43, 127.94[tertiary aromatic carbon atoms], 139.18[quaternary aromatic carbon atom].
1,3-Bis(5-phenyl-1,3-dioxan-2-yl)-benzene (5)
Solid, m.p.=200-202^{0}C. Yield 51%. Anal. Calcd. for $C_{26}H_{26}O_4$: C, 77.61; H 6.46. Found: C, 77.76; H 6.60 ^{1}H-NMR δ (C_6D_6) 3.15[2H,tt, J=10.3, J'=4.6 Hz, 5(5')-H(ax)], 3.69[4H, t(overlapped dd), J=J'=10.3 Hz, 4(4'),6(6')-H(ax)], 4.15[4H, dd, J=10.3 Hz, J'=4.6 Hz, 4(4'), 6(6')-H(eq)], 5.46[2H, s, 2(2')-H(ax)], 6.81(4H, m, aromatic protons), 7.04(6H, m, aromatic protons)-7.31[1H, t (overlapped dd), J=J'=7.7 Hz, 5"-H], 7.75[2H, dd, J=7.7, J'=1.7 Hz, 4"(6")-H], 8.29[1H, t, J=1.7 Hz, 2"-H). ^{13}C-NMR δ (C_6D_6) 41.13$C^{5(5')}$, 71.95$C^{4(4'),6(6')}$, 101.11$C^{2(2')}$, 124.85, 126.61, 127.03, 128.50[tertiary aromatic carbon atoms], 137.97,139.08[quaternary aromatic carbon atoms].
1,3-Bis(5-ethyl-5-methyl-1,3-dioxan-2-yl)-benzene (6)
Solid, m.p.=100-101^{0}C. Yield 49%. Anal. Calcd. for $C_{20}H_{30}O_4$: C, 71.85; H, 8.98. Found: C, 71.98; H 9.11. ^{1}H-NMR δ (C_6D_6) 0.26, 0.27[3H, s, 5(5')-$C\underline{H}_3$(eq)], 0.51, 0.52[3H, t, J=7.3 Hz, 5(5')-CH_2CH_3(eq)], 0.703, 0.711[2H, q, J=7.3 Hz, 5(5')-$C\underline{H}_2CH_3$(eq)], 1.15, 1.16[3H, t, J=7.57 Hz, 5(5')-$CH_2C\underline{H}_3$(ax)], 1.70, 1.71[2H, q, J=7.57 Hz, 5(5')-$C\underline{H}_2CH_3$(ax)], 3.22[2H(ring B), d, J=11.1 Hz, 4(4'),6(6')-H(ax)], 3.28[2H(ring A), d, J=11.1 Hz, 4(4'),6(6')-H(ax)], 3.60[2H(ring A), d, J=11.1 Hz, 4(4'),6(6')-H(ax)], 3.69[2H(ring B), d, J=11.3 Hz, 4(4'), 6(6')-H(eq)], 5.28, 5.29, 5.31, 5.32[2H, s, 2(2')-H(ax)], 7.24[1H, overlapped peaks, 5"-H], 7.68[2H, overlapped peaks, 4"(6")-H], 8.17[1H, overlapped peaks, 2"-H). ^{13}C-NMR δ (C_6D_6) 5.86[5(5')-CH_2CH_3(eq)], 7.75[5(5')-$\underline{C}H_2CH_3$(ax)], 17.66[5(5')-$\underline{C}H_3$(eq)], 19.35[5(5')-CH_3(ax)], 26.73[5(5')-CH_2CH_3(ax)], 28.42[5(5')-CH_2CH_3(eq)], 32.26, 34.88$C^{5(5')}$, 75.16, 76.34$C^{4(4'),6(6')}$, 101.37, 101.59$C^{2(2')}$, 124.62, 126.47, 127.93[tertiary aromatic carbon atoms], 139.15, 139.24[quaternary aromatic carbon atoms].

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