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SYNTHESIS AND STRUCTURAL ANALYSIS OF SOME NEW PRECURSORS OF MACROCYCLIC CYCLOPHANES: 1,4-BIS (2-R-5-R^1-1,3-DIOXAN-2-YL) BENZENE DERIVATIVES

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Dedicated to Professor Sorin Mager
on the occasion of his 75th birthday

ABSTRACT. The synthesis and the stereochemistry of some new 2,5-substituted-1,3-dioxane derivatives of 1,4-diacetylbenzene are reported. The structural analysis carried out using NMR investigations revealed the anancomeric structure of the compounds and the *cis* or/and *trans* disposition of the substituents. These experiments showed the favorable arrangement of the different functions for the participation to the macrocyclisation reactions insured by the axial orthogonal disposition of the aromatic group with respect to both 1,3-dioxane rings.

Introduction

The studies on the conformational equilibriums of 2,2-disubstituted-1,3-dioxanes bearing alkyl and aryl groups in the ketal part of the heterocycle (I, II; *e.g.* 2-phenyl-2-methyl-1,3-dioxanes, Scheme 1) showed the shifting of these equilibriums toward the conformer exhibiting the aryl group in the *axial* position [1-3].

The *axial* preference of the phenyl group is suggested by the higher A value of the methyl group at position 2 (A_{Me} = 16.63 kJ/mol [1]) than the A value of the phenyl group (A_{Ph} = 13.04 kJ/mol [1]) at the same position. Thermodynamic measurements in 2-methyl-2-phenyl-1,3-dioxanes showed a considerably higher preference of the methyl group for the *equatorial* position (ΔG_{II-I}^0 = 10.11 kJ/mol [1]) than that calculated from the A-values of methyl and phenyl groups ($\Delta A = A_{Me} - A_{Ph}$ = 3.63 kJ/mol).

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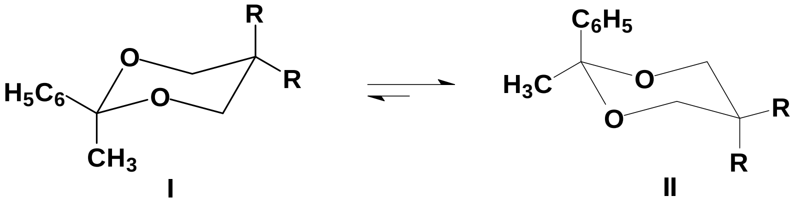
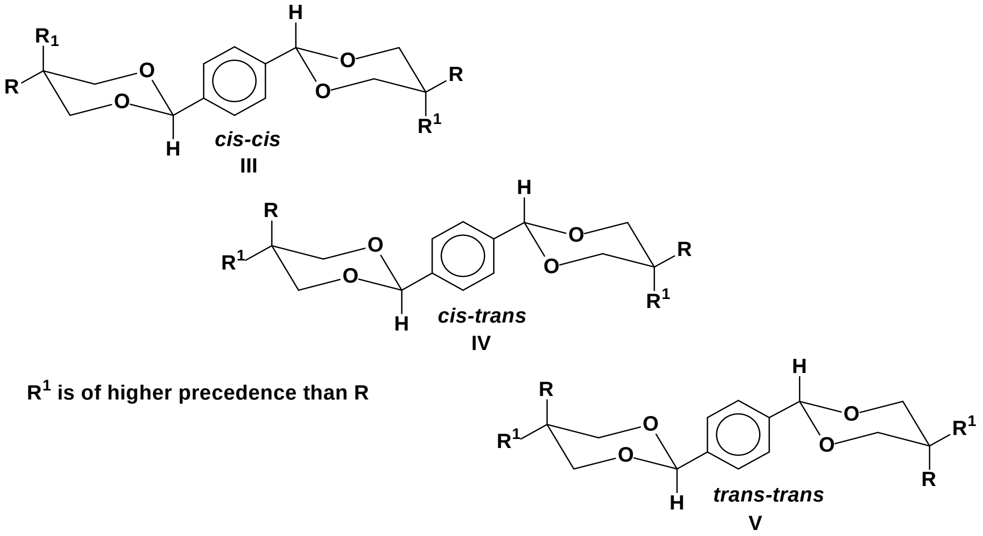


Scheme 1

Investigations on the stereochemistry of compounds bearing two 1,3-dioxane rings on the same aromatic system, obtained from benzenedicarboxaldehydes, have revealed the *equatorial* orientation of the aromatic ring for both heterocycles [4-6], while the investigations on the stereochemistry of derivatives of 1,4-diacetylbenzene [7] and of 2,6-diacetylpyridine [8] showed the axial orthogonal orientation of the aromatic ring with respect to both 1,3-dioxacyclohexane systems. The derivatives of these compounds bearing different substituents in positions 5' and 5" of the 1,3-dioxane rings show three diastereoisomers (*cis,cis*, *cis,trans,* and *trans,trans*) in agreement with the disposition of the groups with higher precedence at positions 5' (5") on the same side (*cis*) or on different sides (*trans*) with the aromatic group at position 2' or 2" (*e.g.* the derivatives of terephthaldialdehyde of scheme 2). Some *cis-cis* 1,3-dioxane derivatives of 1,4-diacetylbenzene and of 2,6-diacetylpyridine were already investigated and they were successfully used in the synthesis of macrocyclic cyclophanes [9, 10].



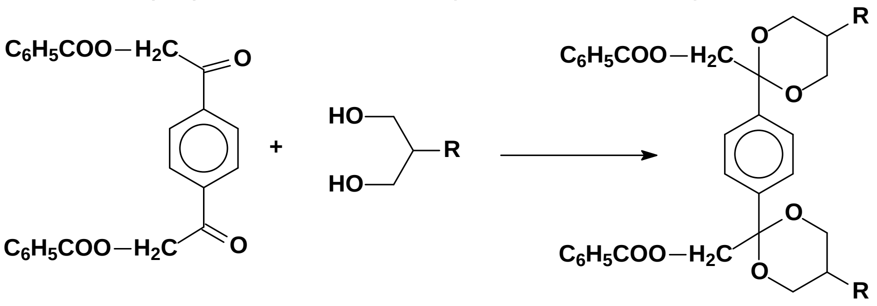
R^1 is of higher precedence than R

Scheme 2

It was considered of interest to investigate the stereochemistry of new 1,3-dioxane derivatives of 1,4-diacetylbenzene (or of some α, α' derivatives) bearing different substituents at the positions 2 and 5 of the 1,3-dioxane rings and to determine the conformational behaviour of the heterocycles, the orientation of the aromatic substituent for both heterocycles, and to identify and to characterize the possible *cis* and *trans* isomers.

Results and Discussions

New 1,3-dioxane derivatives of 1,4-diacetylbenzene having nonsymmetric substitution at the positions 5' and 5" of the heterocycles were obtained in good yields by the condensation reaction of 1,4-dicetylbenzene with several 1,3-propanediol derivatives (Scheme 3, Table 1).



R= $COOCH_3$	**1**	**5**
R=$COOC_2H_5$	**2**	**6**
R = CH_2OH	**3**	**7**
R = CH_2OTs	**4**	**8**

Scheme 3

The yields for the reactions with esters were higher and for all cases the raw products were mixtures of isomers: *cis-cis, cis-trans* and *trans-trans*. The ratios and the yields are presented in table 1. At position 2 we considered as reference the ester group, which is of highest precedence.

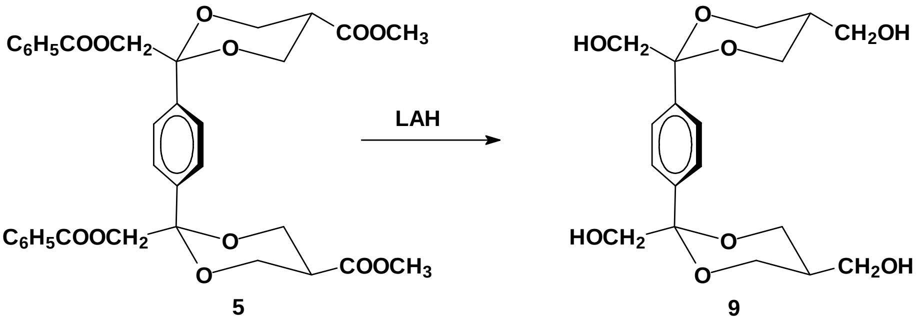
Table 1.

Results of the synthesis of compounds **5-8**

Compound	**5**	**6**	**7**	**8**
Yields	45	49	53	36
Cis-cis/cis-trans/trans-trans	0 / 2 / 1	0 / 2 / 1	10 / 12 / 1	1 / 1.4 / 0

The *trans-trans* isomers of **5** and **6** and *cis-cis* isomer of **7** and **8** were separated by flash chromatography and were investigated as single compounds.

The *trans-trans* isomer of the tetrol **9** was synthesized (yields = 94 %) using the LAH reduction (Scheme 4) of the separated *trans-trans* isomer of **5**.



Scheme 4

The NMR investigation showed the anancomeric structure of the compounds. In all investigated compounds the aromatic substituent occupies the axial orientation for both 1,3-dioxane rings, while the substituents at positions 5' and 5" are either equatorial or axial and generate the *cis* and *trans* configurations. The anancomeric structure of the compounds is proved by the recording in the NMR spectra of different signals for the axial and equatorial protons of the dioxacyclohexane rings (Table 2). The axial or equatorial orientation of the substituents at positions 5' and 5" was deduced from the values of the coupling constants. If the substituent at position 5 of the 1,3-dioxane ring is equatorial, the axial proton at the same position exhibits a large coupling constant with the axial protons of positions 4 and 6. The signal belonging to the axial protons at positions 4 and 6 is in this case a doublet of doublets with two large coupling constants (many times overlapped into a triplet; the second coupling with large constant is due to the geminal equatorial proton). If the substituent at position 5 of the 1,3-dioxane ring is axial, the proton of the position exhibits couplings with small constants with the protons of positions 4 and 6, including the axial ones. The pattern for the signal belonging to the axial protons of positions 4 and 6 shows a doublet of doublets with a large coupling constant (due to the equatorial protons of the same positions) and another one with small value due to the coupling with the vicinal equatorial proton at position 5.

Table 2.

^{1}H NMR data (δ, ppm; J, Hz; $CDCl_3$) for compounds **4-8**

Compd.	Isomer	Position of R at 5'(5")	4'(4")-H, 6'(6")-H (δ)		J		
			ax	eq	4(6)eq-4(6)ax	4(6)ax-5ax	4(6)ax-5eq
5	*trans-trans*	3.61	3.84	4.20	11.7	11.7	-
6	*trans-trans*	1.18(t), 4.06(q)	3.84	4.19	11.7	11.7	-
7	*cis-cis*	3.95-3.96 (overlapped peak)		4.09	11.7	-	2.3
8	*cis-cis*	4.46	3.80 -3.92 (overlapped peak)				
9	*trans-trans*	3.22	4.53	4.96	11.3	11.3	-

Conclusions

The high yields synthesis of some new *cis-cis* and *trans-trans* bis-1,3-dioxane derivatives having as spacer between the two heterocycles an 1,4-phenylene unit is reported. The structural analysis carried out by NMR investigations reveals the axial orientation of the aromatic ring with respect to both dioxacyclohexane units. These derivatives are precursors for the synthesis of simple or layered cyclophanes.

Experimental

^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz), COSY and HMQC spectra, were recorded at *rt* in $CDCl_3$ or MeOD on a Bruker 300 MHz spectrometer, using the solvent line as reference. Mass spectra were recorded on an ATI Unicam Automass.

Melting points were measured with a Kleinfeld melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was conducted on silica gel 60 F_{254} TLC plates purchased from Merck. Preparative column (flash) chromatography was preformed using PharmPrep 60 CC (40-63 μm) silica gel purchased from Merck. Chemicals were purchased from Aldrich or Across and were used without further purification.

General Procedure for the Synthesis of Compounds 5-8

(5 mmol) diols **1-4** and (2 mmol) ketone (1,4-bis(2'-benzoyloxy-acetyl)benzene) with catalytic amounts of *p*-toluenesulphonic acid (0.1 g) were solved in 100 mL $CDCl_3$. The mixture was refluxed and the water produced in the reaction removed using a modified Dean-Stark trap. When 80 % of the water had been separated, the mixture was cooled to room temperature

and the catalyst was neutralized (under stirring 0.5 h) with CH_3-COONa powder in excess (0.2 g). The reaction mixture was washed twice with 100 mL of water. After drying over $MgSO_4$, the solvent was removed and the crude products were purified by flash chromatography or by crystallization.

***t*-1,*t*-4-Bis(*r*-2'-benzoyloxymethyl- *t*-5' – carboxymethyl-1,3-dioxan-2'-yl)benzene (5 *trans-trans*)**
White solid, m.p.=208-9℃, yield 24 % (flash chromatography, eluent: DCM, Rf = 0.24. ^{1}**H-NMR** (300 MHz,$CDCl_3$, δ ppm): 3.14 (2H, m), 3.61 (6H, s), 3.84 (4H, dd overlapped, *J*=*J'*=11.7 Hz), 4.20 (4H, dd, *J*=11.7 Hz, *J'*= 4.6 Hz), 4.36 (4H, s) 7.39 (4H, dd overlapped, *J*=8.7 Hz, *J'*=8.3 Hz), 7.54 (2H, t, *J*=8.7 Hz) 7.56 (4H, s), 7.95 (4H, d, *J* =8.3 Hz). ^{13}**C-NMR** (75 MHz, $CDCl_3$, δ ppm): 40.0 (CH), 52.0 (CH_3), 62.1 (CH_2), 69.8 (CH_2), 100.0 (C_{quat}) 128.4 (CH), 128.7 (CH), 130.0 (C_{quat}), 129.8 (CH), 133.2 (CH) 136.8 (C_{quat}), 165.9 (CO), 170.3 (CO).

***t*-1, *t*-4-Bis(*r* -2'-benzoyloxyethyl-*t*-5'- carboxyethyl-1,3-dioxan-2'-yl)benzene (6 *trans-trans*)**
White solid, m.p.=141-2℃, yield 26 % (flash chromatography, eluent: DCM, Rf = 0.27. ^{1}**H-NMR** (300 MHz,$CDCl_3$, δ ppm): 1.18 (6H, t, *J*=7.2 Hz) 3.11 (2H, m), 3.84 (4H, dd overlapped, *J*=*J'*=11.7 Hz), 4.06 (4H, q, *J*=7.2 Hz) 4.19 (4H, dd, *J*=11.7 Hz, *J'*= 4.5 Hz), 4.36 (4H, s), 7.39 (4H, dd overlapped , *J*=7.9 Hz, *J'*=7.2 Hz) 7.52 (2H, t, *J*=7.9Hz) 7.57 (4H, s), 7.95 (4H, d, *J* =7.2 Hz).

***t*-1,*t* -4- Bis(*r*- 2'-benzoyloxymethyl- *c*-5'-hydroxymethyl-1,3-dioxan-2'-yl)benzene (7 *cis-cis*)**
White solid, m.p.= 154-5℃, yield 17% (flash chromatography, eluent: DCM/ethanol = 2/0.1, Rf = 0.15. ^{1}**H-NMR** (300 MHz,$CDCl_3$, δ ppm): 1.47 (2H, dt *J*=7.2, *J'*=2.3), 1.78 (2H, t, *J*=5.3 Hz), 3.95-3.96 (8H, overlapped picks), 4.08 (4H, dd, *J*= 11.7 Hz, *J*= 4.5 Hz), 4.33 (4H, s), 7.41 (4H, t, *J*= 7.1 Hz) 7.52 (2H, dd overlapped), 7.99 (4H, d, *J*= 7.1 Hz). ^{13}**C-NMR (**75 MHz, $CDCl_3$, δ ppm): 36.2 (CH), 62.05 (CH_2), 62.12 (CH_2), 70.12 (CH_2), 100.3 (C_{quat}), 128.5 (CH), 128.6(CH), 129.8 (CH), 129.9 (C_{quat}), 133.2 (CH), 137.0 (CH), 166.0 (CO).

***t*-1,*t* -4- Bis(*r*- 2'-benzoyloxymethyl- *c*-5'-tosyloxymethyl-1,3-dioxan-2'-yl)benzene (8 *cis-cis*)**
White solid, m.p.=213-4℃, yield 14% (flash chromatography, elution: diethyl ether/ pentane = 1/2, Rf = 0.21. ^{1}**H-NMR** (300 MHz,$CDCl_3$, δ ppm):

1.69 (2H, m), 2.43 (6H, s),C 3.80-3.92 (8H, overlapped picks), 4.21 (4H, s), 4.46 (4H, d, *J*= 7.5 Hz), 7.31 (4H, d, *J*=8.3 Hz) 7.41 (4H, dd, *J*=8.3 Hz, *J*=7.2 Hz) 7.53 (4H, s) 7.55 (2H, t, *J*=7.2 Hz) 7.77 (4H, d, *J*=8.3 Hz) 7.97 (4H, dd, *J*=8.3 Hz) ^{13}**C-NMR (**75 MHz, $CDCl_3$, δ ppm): 21.8 (CH_3), 33.9 (CH), 61.4 (CH_2), 68.9 (CH_2), 69.9 (CH_2), 100.4 (C_{quat}), 128.0 (CH), 128.56(CH), 128.62(CH), 129.8 (CH), 130.1 (CH) 132.8 (C_{quat}), 133.2 (CH), 136.7 (C_{quat}), 145.1 (C_{quat}), 165.9 (CO).

General Procedure for the Synthesis of Compound 9

A mixture of **5** (1mmol) and (5 mmol) of $LiAlH_4$ in 50 mL of THF was stirred under reflux for 5 h. Aqueous NaOH (5%; 10 mL) was very slowly dropped into the stirred mixture at 0-5°C to destroy the excess $LiAlH_4$. After being stirred for 1 h, the mixture was filtered and washed several times with hot THF. The filtrate was evaporated, and the residue was purified by crystallisation from DCM.

***t*-1,*t* -4- Bis(*r*- 2'-benzoyloxymethyl- *t*-5'-hydroxymethyl-1,3-dioxan-2'-yl)benzene (9 *trans-trans*)**

White solid, m.p.= 218-9℃, yield 94%. ^{1}**H-NMR (**300 MHz, MeOD , δ ppm): 2.2-2.35 (2H, m), 3.22 (4H, d, *J*= 6.4 Hz), 3.46 (4H, s) 3.53(4H, dd, *J*=*J'*=11.3 Hz), 3.96 (4H, dd, *J*=11.3 Hz, *J'*=4.6 Hz), 7.49 (4H, s). ^{13}**C-NMR (**75 MHz, MeOD, δ ppm): 40.0 (CH), 62.7 (CH_2), 66.0 (CH_2), 72.4 (CH_2), 103.6 (C_{quat}), 130.8 140.4 (C_{quat}). **MS** (70 eV) (rel. int. %) m/z: 366 (M^+, 0.6), 179 (7), 147 (9), 117 (12), 89 (22), 71 (96), 59(100).

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