

SYNTHESIS AND STEREOCHEMISTRY OF SOME NEW 1,3-DIOXANE DERIVATIVES OF 1,3-DIACETYL BENZENE

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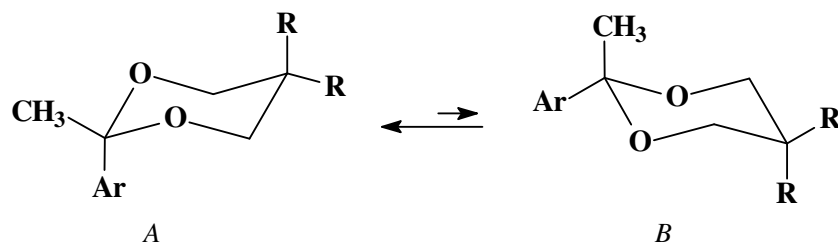
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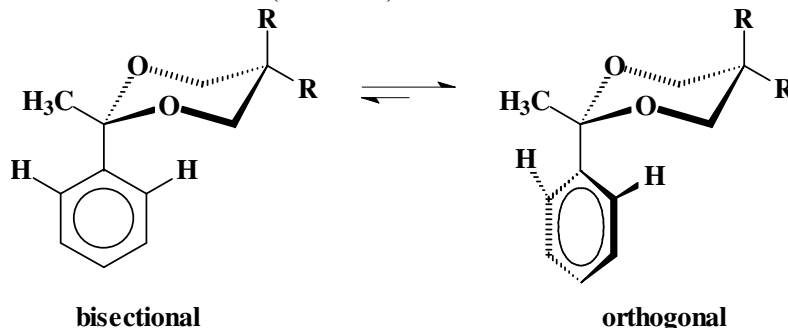
The synthesis, the *cis-trans* isomerism and the conformational analysis of some new 1,3-dioxanes obtained from 1,3-diacetylbenzene are reported.

INTRODUCTION

The studies¹⁻⁴ on the stereochemistry of 2-methyl-2-aryl-1,3-dioxanes showed the shifting of the characteristic conformational equilibrium for the flipping of the heterocycle (Scheme 1) towards the conformation exhibiting the aromatic group in axial orientation (A \longleftrightarrow B).

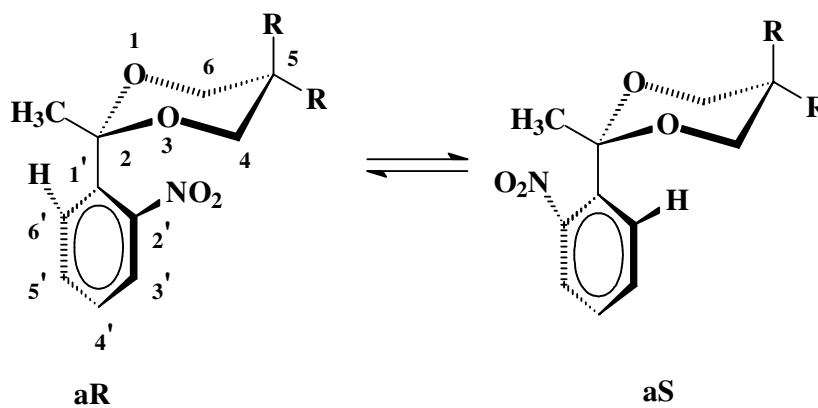


The investigations performed by X-ray diffractometry⁵⁻⁷ and by room temperature (rt) and low temperature NMR spectra^{3,4} showed the high preference of the axial aromatic group for the orthogonal rotamer, either in solid state or in solution (Scheme 2).



The preference in solution for the orthogonal rotamer was proved by the influence of the magnetic anisotropy of the aromatic ring on the chemical shifts of the protons of the 1,3-dioxane ring and of the equatorial groups at the position 5 of the heterocycle. Indeed the orthogonal disposition of the aromatic substituent determines a significant modification of the magnetic environment in different areas of the molecule having as a result the strong shielding of the protons belonging to the equatorial group at position 5 and of the equatorial protons at positions 4 and 6 of the heterocycle.^{3,4}

Despite the preference of the axial aromatic group for the orthogonal orientation (this rotamer is more stable than the bisectonal one) this group exhibits at rt a free rotation (the sterical hindrance is not high enough to freeze the rotation of the aromatic substituent). Interesting data about the rotation of the axial aryl group were obtained by dynamic NMR investigations carried out with compounds bearing disymmetric aromatic substituents.⁴ As an example the *o*-nitrophenyl derivative exhibits a chiral axis ($C^{1'} - C^2$, the reference groups are the hydrogen atom at position 6' and the NO_2 group at one of the ends and the methyl group and the whole heterocycle at the other end of the chiral axis) (Scheme 3).



Scheme 3

The positions 4 and 6 of the 1,3-dioxane ring are in this case diastereotopic but the free rotation of the aromatic ring at rt (enantiomeric inversion) renders equivalent in NMR the protons of these positions and the spectra recorded at rt show unique signals corresponding to the average of the magnetic environments of the diastereotopic positions.

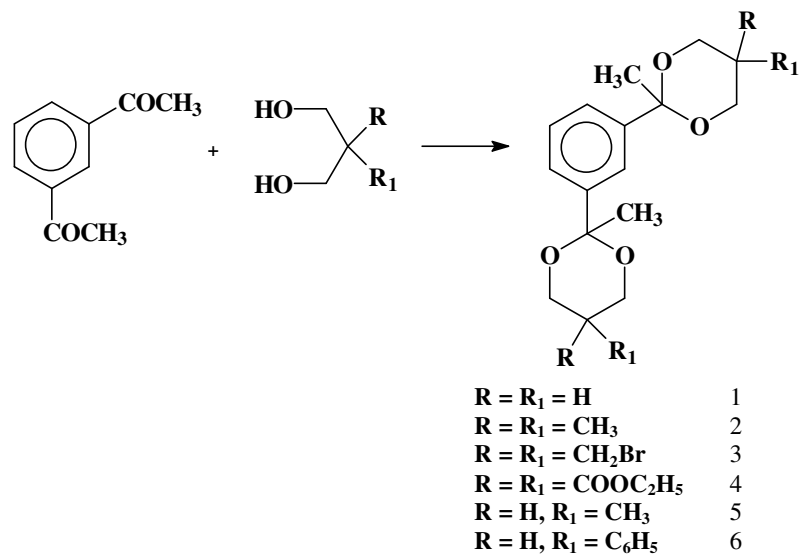
At low temperature the rotation of the aromatic ring is frozen and the NMR spectra exhibit different signals for the protons at positions 4 and 6. The values of the diastereotopicities are relatively high [$(\Delta\delta_{4\text{ax}-6\text{ax}} = 0.08-0.61 \text{ ppm})$; $(\Delta\delta_{4\text{eq}-6\text{eq}} = 0.16-0.27 \text{ ppm})$]⁴.

Investigations⁸⁻¹⁰ carried out with 1,3-dioxane derivatives obtained from benzenedicarboxaldehydes showed anomeric structures with the equatorial orientation of the aromatic group in both heterocycles.

In this work, the results of the investigations concerning the synthesis and the stereochemistry of some new 1,3-dioxane derivatives obtained from 1,3-diacetylbenzene are reported. The investigated structural aspects are considered of interest due to the complex configurational and conformational behavior of the target compounds.

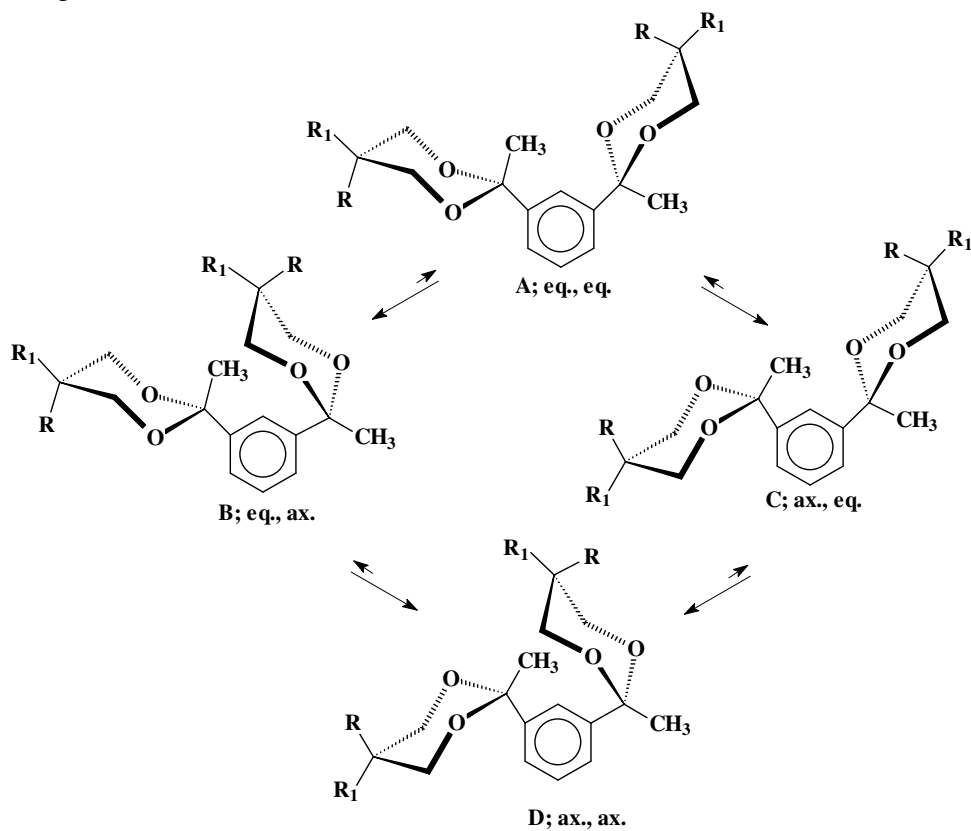
RESULTS AND DISCUSSION

New compounds exhibiting two 1,3-dioxane rings were obtained by the condensation reaction of 1,3-diacetylbenzene with several 1,3-propanediols (Scheme 4).



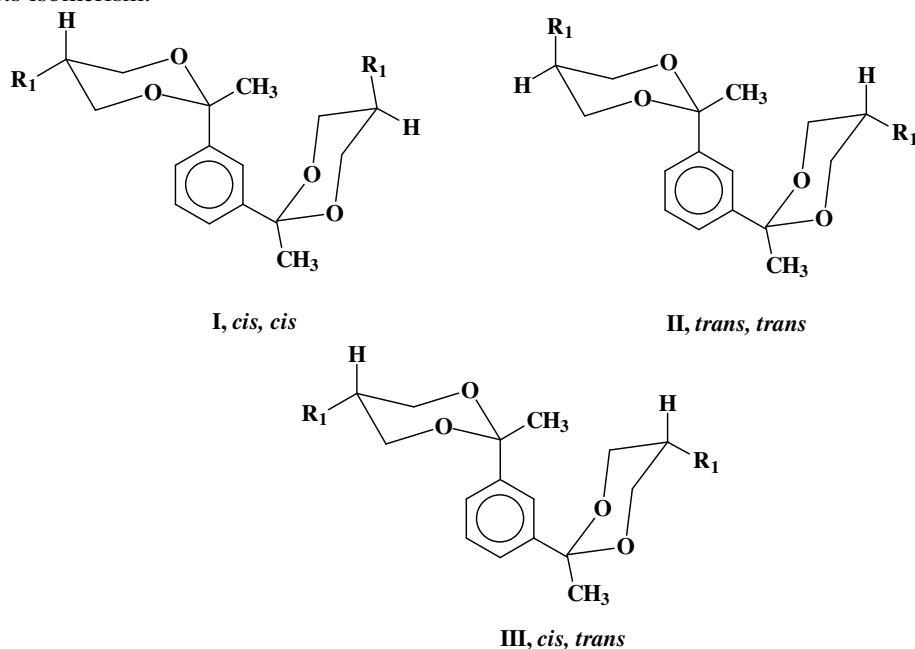
Scheme 4

All the investigated compounds exhibit anancomeric structures, the conformational equilibrium ($A \rightleftharpoons B \rightleftharpoons C \rightleftharpoons D$) for each 1,3-dioxane ring (Schemes 1 and 5) being shifted towards the conformer with axial aromatic substituent. So the 1,3-phenylene group is axial connected to both 1,3-dioxane rings (structure D, Scheme 5).



Scheme 5

Compounds **5** and **6** can exhibit three isomers (*cis,cis*; *cis,trans* and *trans,trans*) in agreement with the disposition of the substituents at the positions 5 and 5' and of the phenylene group at positions 2 and 2' on the same side (*cis*) or on opposite sides (*trans*) of the 1,3-dioxane rings (Scheme 6). Compounds **1-4** do not show *cis-trans* isomerism.

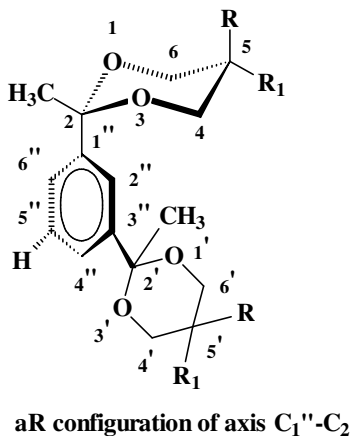


Scheme 6

The isomer with both R_1 (alkyl or aryl) groups in equatorial positions is denoted as I (*cis,cis*), the isomer with both groups in axial orientation as II (*trans,trans*) and structure III (*cis,trans*) exhibits one of the substituents in equatorial position and the other one in axial orientation.

From the three isomers of compounds **5** and **6** the *cis, cis* isomer exhibiting both groups (at positions 5 and 5') in equatorial orientation is the major one and it has been isolated as single compound by crystallization.

The dissymmetry of the aromatic substituent introduces the axial chirality of the investigated compounds. The bonds between the aromatic group and the saturated heterocycles ($C^2-C^{1''}$ and $C^{2'}-C^{3''}$) are chiral axes, the reference groups being the second 1,3-dioxane ring at position 3'' and the H at position 5'' at one of the ends of the considered chiral axis and the methyl group at position 2 and the whole 1,3-dioxane ring at the other end of the chiral axis (Scheme 7).



Scheme 7

The compounds can show *like* (aRaR, aSaS) or *unlike* (aRaS) isomers. Due to the chirality of the molecule, in the frozen structures, positions 4(4') and 6(6') become diastereotopic ones. Due to the fast rotation at rt of the aromatic ring around its bonds with the heterocycles the spectra show a unique set of signals (at means values of the chemical shifts) and the presence of *like* and *unlike* structures and the diastereotopicity of 4(4') and 6(6') positions can not be observed.

The anancomeric structure of the compounds leads to the recording, in the rt NMR spectra, of different signals for the equatorial and axial protons of the 1,3-dioxane rings [positions 4(4') and 6(6')] and for the axial and equatorial protons of the similar groups located at positions 5 (5') (Table 1).

Table 1

¹H-NMR data for compounds **1-6** (C₆D₆, δ ppm)

Compound	4(4'), 6(6')			5(5')			
	eq.	ax.	Δ _{eq-ax}	CH _{2(ax)}	CH _{2(eq)}	CH _{3(ax)}	CH _{3(eq)}
1		3.64		-	-	-	-
2	3.47	3.33	0.14	-	-	1.25	0.26
3*	3.88	3.59	0.29	3.97	3.12	-	-
4*	5.05	3.95	1.1	4.02	3.78	0.91	0.76
5	3.69	3.31	0.38				0.12
6		3.94				-	

* Spectrum run in CDCl₃

All attempts to record the spectra at low temperature have failed because of the very low solubility of the compounds in all the available solvents (CD₂Cl₂, toluene-d₈, acetone-d₆).

CONCLUSIONS

The NMR investigations of new 1,3-dioxane derivatives obtained from 1,3-diacetylbenzene revealed the anancomeric structure of all reported compounds. The major isomers (*cis-cis*) of compounds **5** and **6** were separated and investigated as single isomers. The axial position of the aromatic ring for both heterocycles was deduced by the equivalence in NMR of the two heterocycles and by the high shielding of the equatorial protons at positions 4(4') and 6(6') and of the protons belonging to the equatorial groups at the positions 5(5').

EXPERIMENTAL

General: ¹H and ¹³C-NMR spectra were recorded at rt, using C₆D₆ or CDCl₃ as solvent, in 5 mm tubes, on a Bruker AM 400 Fourier transform NMR spectrometer, equipped with a dual ¹³C-H head, operating at 400 MHz for protons and 100 MHz for carbon atoms.

Melting points were measured with an Electrothermal melting point apparatus and are uncorrected.

Compounds 1-6, general procedure: Stoichiometric amounts of 1,3-diacetylbenzene (0.1 mol) and 1,3-diol (0.2 mol), with catalytic amounts of p-toluenesulphonic acid (0.1 g) were solved in 200 mL benzene. The mixture was refluxed and the resulted water was separated in a Dean-Stark trap. When 80% of the theoretical water was separated, after cooling at rt, the catalyst was neutralized (with CH₃COONa powder in excess – 0.2 g, under stirring 0.5 h). The reaction mixture was washed twice with 100 mL water. After drying (with Na₂SO₄) the benzene was removed and the 1,3-dioxane compounds were purified by crystallization from ethanol.

1,3-Bis-(2-methyl -1,3-dioxan-2-yl)-benzene **1**

White crystals, m.p. = 165-166^oC. Yield = 42%. Anal.calcd. for C₁₆H₂₂O₄: C 69.12%, H 7.97%; found C 69.35%, H 8.12%

¹H-RMN (C₆D₆) δ: 0.68 [2H, m, 5(5')-H_{eq}], 1.75 [6H, s, 2(2')-CH₃], 1.82-1.92 [2H, m, 5(5')-H_{ax}], 3.64 [8H, overlapped peaks, 4(4'),6(6')-H], 7.33 [1H, t (overlapped dd), J = J' = 7.6 Hz, 5''-H], 7.50 [2H, dd, J = 7.7 Hz, J' = 1.2 Hz, 4''(6'')-H], 7.90 (1H, s, 2''-H),

¹³C-RMN (C₆D₆) δ: 20.36 C^{5(5')}, 27.45 [2(2')-CH₃], 55.63 C^{4(4'),6(6')}, 95.34 C^{2,(2')}, 120.31, 121.01, 123.93 (tertiary aromatic carbon atoms), 137.43 (quaternary aromatic carbon atom).

1,3-Bis-(2,5,5-trimethyl -1,3-dioxan-2-yl)-benzene **2**

White crystals, m.p. = 94-96^oC. Yield = 58%. Anal.calcd. for C₂₀H₃₀O₄: C 71.90%, H 9.05%; found C 71.76%, H 8.87%.

$^1\text{H-RMN}$ (C_6D_6) δ : 0.26 [6H, s, 5(5')- $\text{CH}_3(\text{eq})$], 1.25[6H, s, 5,5'- $\text{CH}_3(\text{ax})$], 1.77 [6H, s, 2(2')- CH_3], 3.33 [4H, d, J = 10.8 Hz, 4(4'),6(6')- H_{ax}], 3.47 [4H, d, J = 10.8 Hz, 4(4'),6(6')- H_{eq}], 7.34 [1H, t (overlapped dd), J = J' = 7.6 Hz, 5''-H], 7.54 [2H, dd, J = 7.7 Hz, J' = 1.7 Hz, 4''(6'')-H], 7.88 (1H, s, 2''-H).

$^{13}\text{C-RMN}$ (C_6D_6) δ : 16.23 [5(5')- $\text{CH}_3(\text{eq})$], 17.55 [5(5')- $\text{CH}_3(\text{ax})$], 24.43 $\text{C}^{5(5')}$, 26.96 [2(2')- CH_3], 66.25 $\text{C}^{4(4'),6(6')}$, 95.11 $\text{C}^{2(2')}$, 120.19, 121.08, 123.85 (tertiary aromatic carbon atoms), 137.11 (quaternary aromatic carbon atom).

1, 3-Bis-(2-methyl-5,5-bis-(bromomethyl) -1,3-dioxan-2-yl)-benzene **3**

White crystals, m.p. = 133-136°C. Yield = 68%. Anal. calcd. for $\text{C}_{20}\text{H}_{26}\text{O}_4$: C 70.54%, H 8.56%; found C 70.31%, H 8.44%.

$^1\text{H-RMN}$ (CDCl_3) δ : 1.56 [6H, s, 2(2')- CH_3], 3.12 [4H, s, 5(5')- $\text{CH}_2\text{Br}(\text{eq})$], 3.97 [4H, s, 5(5')- $\text{CH}_2\text{Br}(\text{ax})$], 3.59 [4H, d, J = 11.5 Hz, 4(4'),6(6')- H_{ax}], 3.88 [4H, d, J = 11.5 Hz, 4(4'),6(6')- H_{eq}], 7.45 [1H, t (overlapped dd)], J = J' = 7.8 Hz, 5''-H] 7.38 [2H, dd, J = 7.7 Hz, J' = 1.1 Hz, 4''(6'')-H], 7.46 [1H, s, 2''-H],

$^{13}\text{C-RMN}$ (CDCl_3) δ : 34.82 [5(5')- $\text{CH}_2\text{-Br}(\text{eq})$], 35.03 [5(5')- $\text{CH}_2\text{-Br}(\text{ax})$], 37.55 [$\text{C}^{5(5')}$], 77.09 [$\text{C}^{4(4'), 6(6')}$], 118 [$\text{C}^{2(2')}$], 124.55, 126.47, 129.69 (tertiary aromatic carbon atoms), 181.93 (quaternary aromatic carbon atom).

1,3-Bis-(2-methyl-5,5-diethoxycarbonyl-1,3-dioxan-2-yl)-benzene **4**

White crystals, m.p. = 68°C, Yield = 63%. Anal. calcd. for $\text{C}_{26}\text{H}_{34}\text{O}_{12}$: C 57.99%, H 6.31%; found C 57.76%, H 6.18%.

$^1\text{H-RMN}$ (CDCl_3) δ : 0.79 [6H, t, J = 7.1 Hz, 5(5')- $\text{COOCH}_2\text{CH}_3(\text{eq})$], 0.91 [6H, t, J = 7.1 Hz, 5(5')- $\text{COOCH}_2\text{CH}_3(\text{ax})$], 3.78 [4H, q, J = 7.1 Hz, 5(5')- $\text{COOCH}_2\text{CH}_3(\text{eq})$], 3.95 [4H, dd, J = 11.5 Hz, J' = 1.3 Hz, 4(4'),6(6')- H_{ax}], 4.02 [4H, q, J = 7.1 Hz, 5(5')- $\text{COOCH}_2\text{CH}_3(\text{ax})$], 5.05 [4H, d, J = 11.5 Hz, 4(4'),6(6')- H_{eq}], 5.19 [2H, s, 2(2')-H], 7.12 [1H, t (overlapped dd), J = J' = 7.7 Hz, 5''-H], 7.33 [2H, dd, J = 7.7 Hz, J = 0.9 Hz, 4''(6'')-H], 7.66 [1H, s, 2''-H],

$^{13}\text{C-RMN}$ (CDCl_3) δ : 13.83 [5(5')- $\text{COOCH}_2\text{CH}_3(\text{eq})$], 13.91 [5(5')- $\text{COOCH}_2\text{CH}_3(\text{ax})$], 53.71 $\text{C}^{5(5')}$, 61.70 [5(5')- $\text{COOCH}_2\text{CH}_3(\text{eq})$], 61.92 [5(5')- $\text{COOCH}_2\text{CH}_3(\text{ax})$], 69.84 $\text{C}^{4(4'),6(6')}$, 101.56 $\text{C}^{2(2')}$, 125.08, 127.74, 128.063, 128.3 (tertiary aromatic carbon atoms), 138.35 (quaternary aromatic carbon atom), 167.06 [5(5')- $\text{COOCH}_2\text{CH}_3(\text{eq})$], 167.10 [5(5')- $\text{COOCH}_2\text{CH}_3(\text{ax})$].

1,3-Bis-(2,5-dimethyl -1,3-dioxan-2-yl)-benzene **5**

White crystals, m.p. = 127-129°C. Yield = 57%. Anal. calcd. for $\text{C}_{18}\text{H}_{26}\text{O}_4$: C 70.51%, H 8.56%; found C 70.39%, H 8.44%

$^1\text{H-RMN}$ (C_6D_6) δ : 0.12 [6H, d, J = 6.7 Hz, 5(5')- CH_3], 1.79 [6H, s, 2(2')- CH_3], 2.04 [2H, m, 5(5')-H], 3.31 [4H, t, overlapped dd, J = J' = 11.4 Hz, 4(4'),6(6') H_{ax}], 3.69 [4H, dd, J = 11.4 Hz, J' = 4.5 Hz, 4(4'),6(6')- H_{eq}], 7.34 [1H, t (overlapped dd), J = J' = 7.7 Hz, 5''-H], 7.53 [2H, dd, J = 7.7 Hz, J' = 1.7 Hz, 4''(6'')-H], 7.70 (1H, s, 2''-H).

$^{13}\text{C-RMN}$ (C_6D_6) δ : 6.66 [5(5')- CH_3], 24.05 $\text{C}^{5(5')}$, 27.57 [2(2')- CH_3], 62.27[$\text{C}^{4(4'),6(6')}$], 95.07 $\text{C}^{2(2')}$, 120.43, 121.14, 124.02 (tertiary aromatic carbon atoms), 137.32 (quaternary aromatic carbon atom).

1,3-Bis-(2-methyl-5-phenyl -1,3-dioxan-2-yl)-benzene **6**

White crystals, m.p. = 105-107°C. Yield = 58%. $\text{C}_{28}\text{H}_{30}\text{O}_4$. Anal. calcd. for $\text{C}_{28}\text{H}_{30}\text{O}_4$: C 78.09%, H 7.03%; found C 78.26%, H 7.15%

$^1\text{H-RMN}$ (C_6D_6) δ : 1.83 [6H, s, 2(2')- CH_3], 3.27 [2H, m, 5(5')-H], 3.94 (8H, overlapped peaks, 4(4'),6(6')-H], 6.72 (6H, m, aromatic protons), 6.96 (4H, m, aromatic protons), 7.35 [1H, t (overlapped dd), J = J' = 7.7 Hz, 5''-H], 7.54 [2H, dd, J = 7.7 Hz, J' = 0.9 Hz, 4''(6'')-H], 8.03 (1H, s, 2''-H).

$^{13}\text{C-RMN}$ (C_6D_6) δ : 27.37 [2(2')- CH_3], 36.00 $\text{C}^{5(5')}$, 61.10 [$\text{C}^{4(4'),6(6')}$], 95.29 $\text{C}^{2(2')}$, 120.58, 121.33, 121.73, 123.34, 124.40 (tertiary aromatic carbon atoms), 133.20, 137.32 (quaternary aromatic carbon atom).

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