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SYNTHESIS, SEPARATION AND X-RAY DIFFRACTOMETRY INVESTIGATIONS OF *TRANS, TRANS* 1,4-BIS(5'-HYDROXYMETHYL-2',5'-DIMETHYL-1',3'-DIOXAN-2'-YL)BENZENE

MONICA CÎRCU, VLAD NISTE, RICHARD ATTILA VARGA,
EMESE DÉNES, ELENA BOGDAN, CRINA CISMAŞ
AND ION GROSU[*]

ABSTRACT. The isolation of pure *trans - trans* isomer of 1,4-(2,5,5-trimethyl-5,5-dihydroxymethyl-1,3-dioxan-2-yl)benzene *via* *O*-protection, column chromatography then deprotection followed by determination of its structure by solid state X-ray diffractometry are reported.

Keywords: *1,3-dioxanes, X-ray structure, supramolecular C-H-π interactions*

INTRODUCTION

The stereochemistry of compounds bearing two or even three 1,3-dioxane rings attached to the same aromatic group was largely investigated by our group and the preference of the aromatic substituent either for the equatorial or axial orientation was observed [1-7].

The derivatives in which the aromatic unit is the unique substituent at the position 2 of the 1,3-dioxane ring (*i.e.* in compounds obtained by the acetalization of aromatic dialdehydes) exhibited the aromatic ligand in equatorial positions. In contrast, the simultaneous presence of methyl and aryl groups at the position 2 of the 1,3-dioxane units (in compounds obtained by the acetalization of 1,4-diacetylarenes) determines the axial orientation of the aromatic substituent (Chart 1).

These results were in agreement with literature data which predict, at the position 2 of the 1,3-dioxane ring, higher A-values for alkyl groups than for the aromatic ones [8-12].

Compounds possessing identical groups at position 5 of the 1,3-dioxane rings do not exhibit diastereomerism, whereas in the case of the derivatives having different groups at position 5, *cis-cis*, *trans-cis* and *cis-cis* steric relationships are possible (Chart 2).

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[*] *Babeş-Bolyai University, Faculty of Chemistry and Chemical Engineering, 11 Arany Janos str., RO-400028 Cluj-Napoca, Roumania, igrosu@chem.ubbcluj.ro*

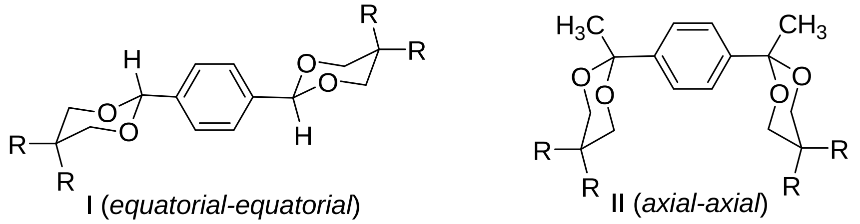


Chart 1. Bis(1,3-dioxan-2-yl)arenes with equatorial-equatorial (I) and axial-axial (II) orientations of the aromatic groups (see above).

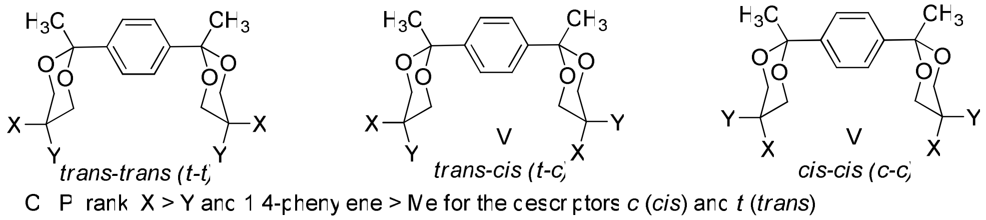


Chart 2. *Trans-trans* (III), *trans-cis* (IV) and *cis-cis* (V) diastereomers of 1,4-bis(2-methyl-5-X-5-Y-1,3-dioxan-2-yl)benzene

Recently, *cis-cis* stereoisomers of some bis(1,3-dioxan-2-yl)arenes bearing equatorial hydroxymethyl functionalities at position 5 were isolated, then successfully used in the syntheses of molecular machines with cyclophane motifs [13,14].

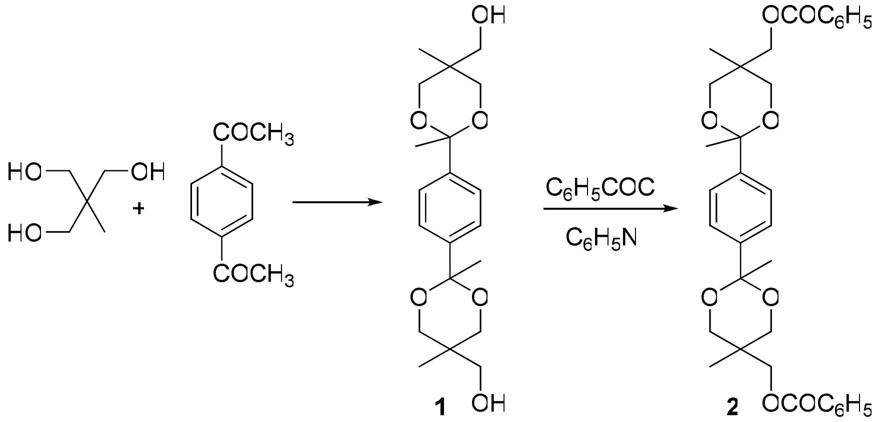
Hence, we considered of outstanding interest to also separate the *trans-trans* isomer of 1,4-(2,5,5-trimethyl-5,5-dihydroxymethyl-1,3-dioxan-2-yl)benzene of type **III** (*t-t*) (X = CH_2OH, Y = Me), to investigate its structure and to predict the possibilities to use this diastereomer as building block in cyclophanes synthesis.

RESULTS AND DISCUSSION

The synthesis of the diastereomeric mixture of 1,4-(2,5,5-trimethyl-5,5-dihydroxymethyl-1,3-dioxan-2-yl)benzenes **1** (Scheme 1) was carried out following a previously described procedure [5, 15]. Thus, in agreement with literature data [5,15] the *trans-trans* isomer of **1** was indeed the major component (60%) of the above mixture as the *cis-trans* and *cis-cis* analogous were obtained in smaller amounts.

The spatial disposal of the *cis-cis* isomer of **1** was previously considered the most appropriate to be used for further macrocyclization.

However, the separation of **1** (*c-c*) could not be carried out neither by crystallization nor by column chromatography since the solubility of these diols in usual solvents was low. In addition, not only that the NMR spectra of the mixture **1** (*c-c*), **1** (*c-t*) and **1** (*t-t*) exhibited many non-separable signals but also their individual appearance was very similar.

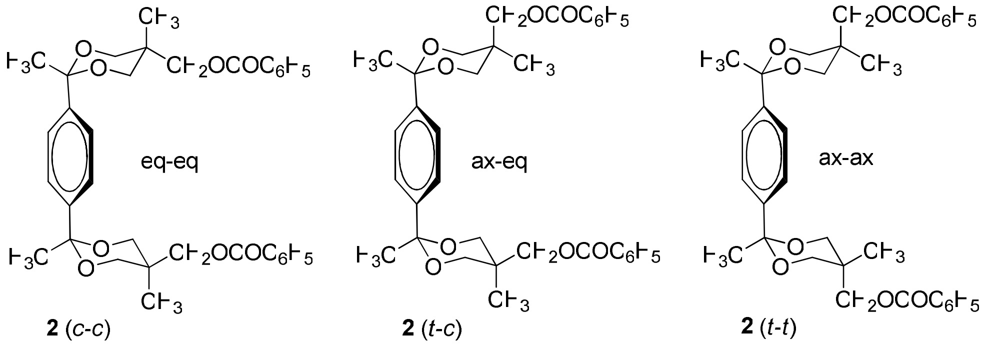


mixture of *t-t*, *t-c* and *c-c* isomers

Scheme 1

In order to avoid these problems, the mixture of stereoisomers of diol **1** was converted into the corresponding mixture of diesters upon benzoylation with benzoyl chloride. The ^{1}H NMR signals of the new mixture of diastereomeric diesters were well separated allowing easily the individual assignment of **1** (*c-c*), **1** (*c-t*) and **1** (*t-t*) [13,15].

Next, the *cis-cis* diastereomer of **2, 2** (*c-c*) (Scheme 2) could be isolated simply as pure compound by repetitive crystallizations from diethylether. Then, its LiOH hydrolysis gave the *cis-cis* diol **2** (*c-c*) as unique isomer in good yields [13, 15].

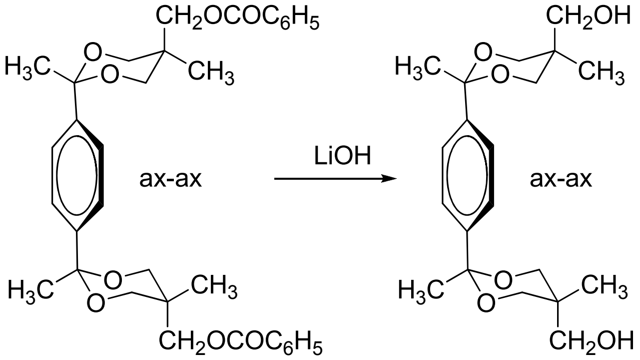


Scheme 2

In contrast, the *axial-axial* diester **2** (*t-t*) could not be isolated as single compound during the work-up described above [15].

Therefore, in the present study, we carried out the isolation of the *trans-trans* diester **2** (*t-t*) (Scheme 2) by column chromatography (eluent ethyl acetate: petroleum ether 1:1) and we investigated it as unique structure.

Then, as above, by LiOH deprotection (Scheme 3) we did succeed the obtention of the *trans-trans* diol **1** (*t-t*) as a single compound. Its structure was fully confirmed by NMR and its molecular structure provided by X-ray diffractometry.



2 (*trans-trans*) **1** (*trans-trans*)

Scheme 3

As expected, the later X-ray diffractometry molecular structure (Figure 1) revealed, the axial orientation of the phenylene and hydroxymethyl groups together with the opposite orientation of the 1,3-dioxane rings with respect to the plane of the aromatic linker.

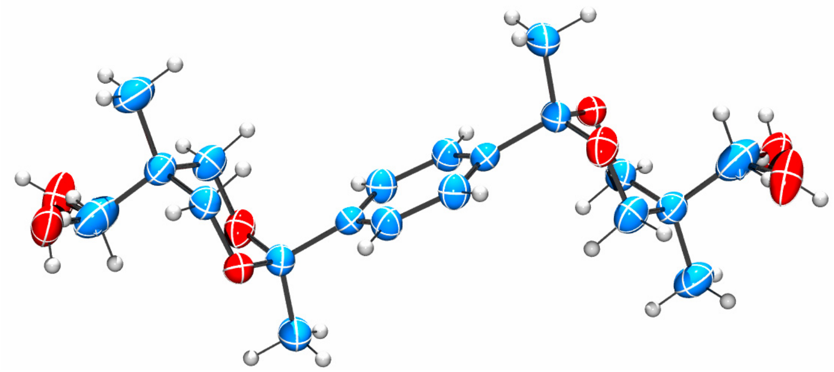


Figure 1. ORTEP diagram for the *trans-trans* diastereomer of **1**.

The phenylene ring exhibited an expected twice orthogonal rotameric orientation (the torsion angle CH_3-$C^{2'}$-C_{ar}-C_{ortho} = 87.37°). The hydroxymethyl groups displaed a “hydrogen inside” conformation and this arrangement generateed two diastereomeric arrangements, namely *syn* and *anti*.

One must observe that, do to the opposite sense of the 1,4-phenylene connection, the *syn* isomer is chiral, exhibiting both its OH groups on the same part of the plane containing the carbon atoms at the 1,3-dioxanic positions 2 and 5 being perpendicular on the aromatic ring. Conversely, the *anti* isomer is centrosymmetric, hence achiral, and disclosed the hydroxy groups on opposite sides of considered plane (Chart 3).

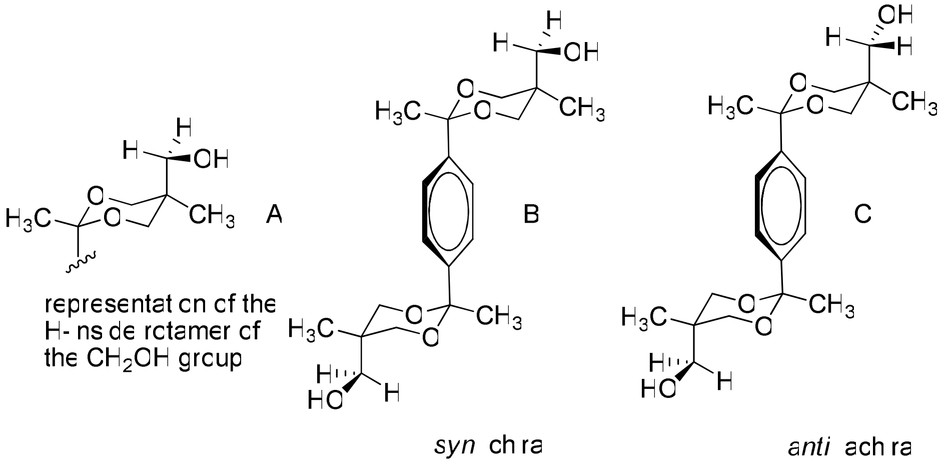


Chart 3. Representations of the H-inside rotamer (A) of the axial CH_2OH group and of the *syn* (B) and *anti* (C) isomers of **1** (*trans-trans*).

In the crystal, all stereoisomers, (±)*syn* and *anti*, were present and, as a consequence, when the structure of the compound was solved at each position, both orientations of the OH group exhibited the same probability, 50 % (Figure 1).

In the lattice (Figure 2), the formation of linear polymers along the c axis by C-H----π interactions involving the hydrogen atoms of the methyl groups at 1,3-dioxanic positions 2 and the aromatic rings were observed (Figure 2). Each aromatic unit is connected on both sides with the methyl groups of the neighbouring molecules. The distances from the H atoms of the methyl group of one molecule to the centroid of the aromatic ring of the partner molecule are d = 3.253, 3.648 and 3.714 Å.

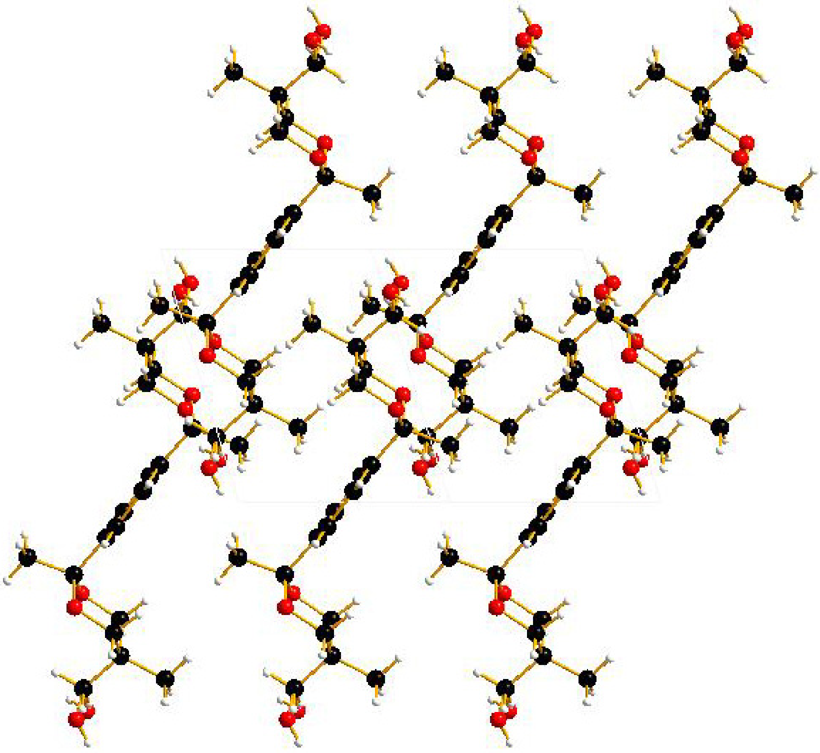


Figure 2. View (along the axis c) of the lattice of **1** (*trans-trans*)

CONCLUSIONS

The *trans-trans* isomer of 1,4-(2,5,5-trimethyl-5,5-dihydroxymethyl-1,3-dioxan-2-yl)benzene **1**, was isolated by column chromatography *via* its dibenzoyl derivative and its structure was determined by X-ray diffractometry. The solid state molecular structure revealed the axial orientation of the aromatic and of the hydroxymethyl groups. In the lattice, all aromatic rings were parallel and the formation of a linear polymer by C-H - π interactions involving the protons of the equatorial methyl groups at positions 2', 2" and the aromatic rings was observed.

EXPERIMENTAL SECTION

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$. APCI MS were recorded on ion trap spectrometer in positive mode. Melting points are uncorrected. Thin layer chromatography (TLC) was carried out on aluminium sheets coated with silica gel 60 F_{254} using UV and $KMnO_4$ visualization.

X-Ray data were collected at room temperature (297 K) using graphite-monochromated MoKα radiation. The structures were refined with anisotropic thermal parameters. The hydrogen atoms were refined with a riding model and a mutual isotropic thermal parameter. For structure solving and refinement the software package SHELX-97 was used.[16,17] The drawings were created with Ortep[18] and Diamond programs.[19]

1,4-(2’,5’,5’-trimethyl-5’,5’-dihydroxymethyl-1’,3’-dioxan-2’-yl)benzene (1)

The benzoylated ester **2** (2 mmol, 1.15 g) was dissolved in a mixture of THF (400 ml), MeOH (40 ml) and H_2O (20 ml) and cooled to 0 ^{o}C. LiOH (5 mmol, 0.210 g LiOHxH_2O) was added and the mixture was stirred at 0 ^{o}C until the complete saponification of the ester occured (TLC monitoring). The solvents were evaporated and the crude product was dissolved in 50 ml diethyl ether and washed with brine. The organic phase was dried over anhydrous sodium sulphate and concentrated to dryness afford the desired product in 98% yield.

The desired *trans-trans* isomer was obtained as white solid, m.p.= 232-233^{0}C. *Calculated for* $C_{20}H_{30}O_6$ *(366.45): C, 65.55; H, 8.25; Found: C, 65.72; H, 8.40.*

^{1}**H-NMR:** (300 MHz, $CDCl_3$) δ ppm: 0.61 [s, 6H, 5’-$CH_{3(eq)}$], 1.53 (s, 6H, 2’-CH_3), 1.68 (t, *J* = 5.2 Hz, 2H, 5’-CH_2-O$\underline{H}$), 3.47 (d, *J* = 11.6 Hz, 4H, 4’-H_{ax}, 6’-H_{ax}), 3.68 (d, *J* = 11.6 Hz, 4H, 4’-H_{eq}, 6’-H_{eq}), 3.91 (d, *J* = 5.2 Hz, 4H, 5’-CH_2), 7.43 (s, 4H, 2-H, 3-H, 5-H, 6-H, 1,4-phenylene).

^{13}**C-NMR:** (75 MHz, $CDCl_3$) δ ppm: 17.0 (5’-CH_3), 32.1 (2’-CH_3), 34.6 (5’-C), 65.7 (5’-CH_2), 67.4 (4’-C, 6’-C), 100.4 (2’-C), 127.1 (2-C, 3-C, 5-C, 6-C), 140.0 (1-C, 4-C).

APCI-MS: m/z = 367 ($[M+H]^+$).

1,4-(2’,5’,5’-trimethyl-5’,5’-benzoyloxymethyl-1’,3’-dioxan-2’-yl)benzene (2)

To a solution of C_6H_5COCl (20 ml) in dry pyridine (100ml) 1,4-(2,5,5-trimethyl-5,5-dihydroxymethyl-1,3-dioxan-2-yl)benzene **1** (10 mmol, 3,66 g) was added. The reaction mixture was stirred for 24 hours at room temperature. After removing the solvent, the crude product was dissolved in dichloromethane (100 ml), washed with aq. 10% NaOH (10%), H_2O (100 ml) and HCl solution (2%), then concentrated to dryness. The crude product was subjected to column chromatography using petroleum ether/ethyl acetate 2/1 as a mobile phase. The desired isomer, *trans-trans* (R_f = 0.32) was obtained as white solid (m.p. = 235-236^{o}C) in 30% yield.

Calculated for $C_{34}H_{38}O_8$ *(574.66): C, 71.06; H, 6.67; Found: C, 70.89; H, 6.95.*

^{1}**H-NMR:** (300MHz, $CDCl_3$) δ ppm: 0.70 [s, 6H, 5’-$CH_{3(eq)}$], 1.54 (s, 6H, 2’-CH_3), 3.53 (d, *J* = 11.0 Hz, 4H, 4’-H_{ax}, 6’-H_{ax}), 3.78 (d, *J* = 11.0 Hz, 4H, 4’-H_{eq}, 6’-H_{eq}), 4.62 (s, 4H, 5’-CH_2), 7.41-7.49 (overlaped signals, 8H, 2-H, 3-H, 5-H, 6-H, *m*-H), 7.54 (multiplet, 2H, *p*-H), 8.04 (d, *J* = 7.1 Hz, 4H, *o*-H).

^{13}C-NMR: (75 MHz, $CDCl_3$) δ ppm: 17.7 (5'-CH_3), 32.4 (2'-CH_3), 34.1 (5'-C), 67.4 (5'-CH_2), 67.8 (4'-C, 6'-C), 101.0 (2'-C), 127.5 (2-C, 3-C, 5-C, 6-C), 128.73 (*m*-C), 129.9 (*o*-C), 130.6 (C quaternary aromatic), 133.3 (*p*-C), 140.3 (1-C, 4-C), 166.9 (5'-CH_2-O-$\underline{C}$O-).

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