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SYNTHESIS AND STEREOCHEMISTRY OF A NEW SERIES OF 2,2'-DISUBSTITUTED-5,5-BIS(BROMOMETHYL)-1,3-DIOXANES

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ABSTRACT. The synthesis of a new series of 2,2'-disubstituted-5,5-bis(bromomethyl)-1,3-dioxanes is reported. The stereochemistry of the products was studied using NMR spectra. These compounds present flexible, semi-flexible and anancomeric structures in solution at room temperature.

INTRODUCTION

Cyclic disulfides have become interesting motifs in nanotechnologies, being used especially as adsorbents on gold surfaces,[1] or on colloidal gold.[2] Our strategy for obtaining a new series of cyclic disulfides is based on the synthesis of bis(bromomethyl) derivatives as intermediates. Some interesting features revealed by NMR spectroscopy have prompted us to extend the number and the type of bis(bromomethyl)-1,3-dioxane derivatives.

RESULTS AND DISCUSSION

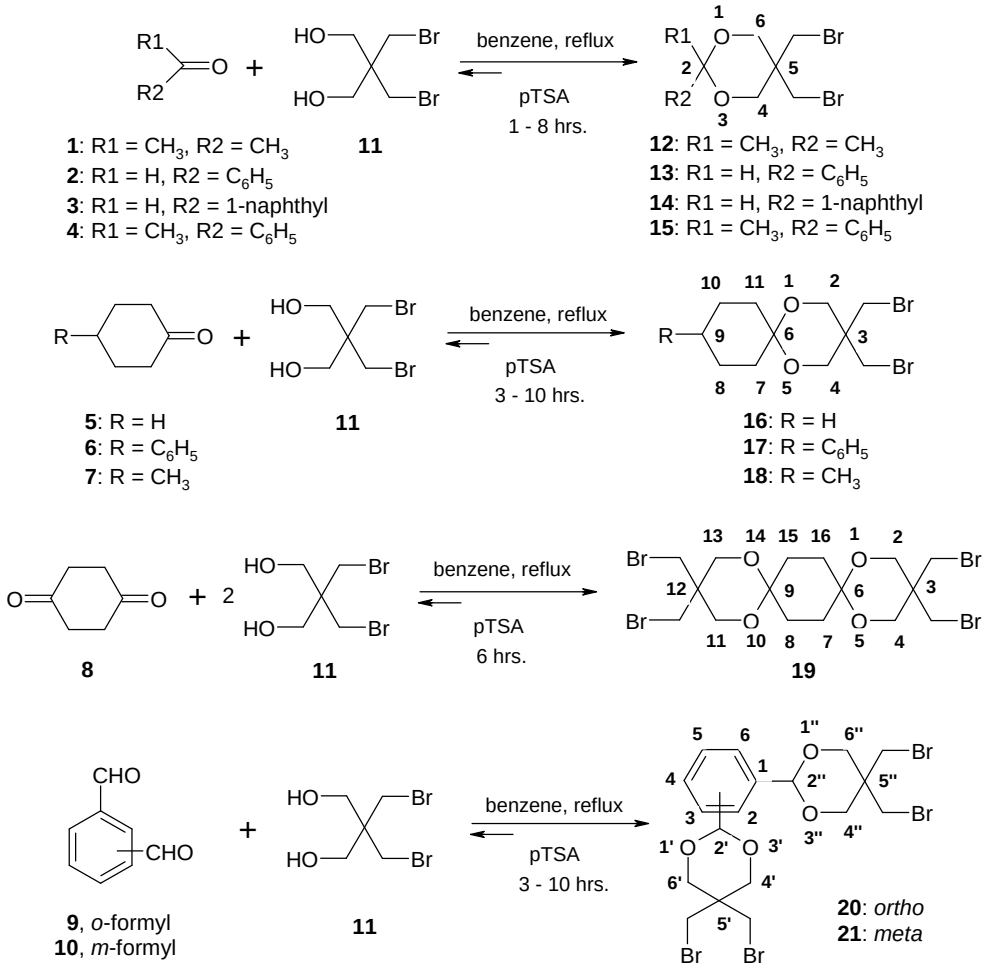
The Synthesis

The title compounds were obtained by acid catalyzed (a)cetalization[3] of the starting carbonyl compounds **1**-**10** with 2,2-bis(bromomethyl)-1,3-propanediol in good and very good yields. The reaction equilibrium was shifted to products by azeotropic distillation of the resulted water with solvent (benzene or toluene, Scheme 1).

The assigned structures were confirmed by NMR spectra. As a general observation, the (a)cetalization had as effect a general shifting to upfield higher fields of the signals corresponding to the starting carbonyls, especially of the acetalic proton or of the α–methyl or methylene group in the case of ketones (**1**, **4**-**8**).

The Stereochemistry of the Products

The structure of **12**, **16** and **19** is flexible due to the symmetrically substitution pattern of the 1,3-dioxane and of the carbocycle rings. The conformational equilibrium between the two chair conformers of the 1,3-dioxane ring (Scheme 2) causes in the ^{1}H-NMR spectrum of **12** the appearance of singlet signals for the protons of 1,3-dioxane and of its substituents at mediated values ($\delta_{2\text{-Me}}$=1.41, $\delta_{5\text{-MeBr}}$=3.58 and $\delta_{4,6}$=3.80 ppm).



1: R1 = CH_3, R2 = CH_3
2: R1 = H, R2 = C_6H_5
3: R1 = H, R2 = 1-naphthyl
4: R1 = CH_3, R2 = C_6H_5

11

12: R1 = CH_3, R2 = CH_3
13: R1 = H, R2 = C_6H_5
14: R1 = H, R2 = 1-naphthyl
15: R1 = CH_3, R2 = C_6H_5

5: R = H
6: R = C_6H_5
7: R = CH_3

16: R = H
17: R = C_6H_5
18: R = CH_3

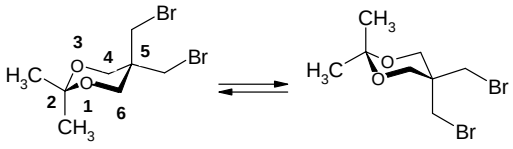
8

19

9, *o*-formyl
10, *m*-formyl

20: *ortho*
21: *meta*

Scheme 1

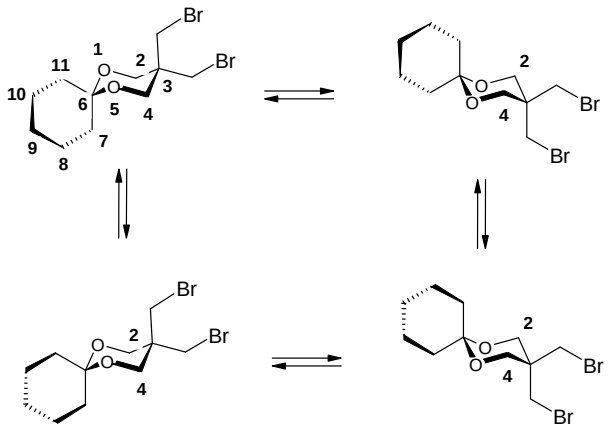


12

Scheme 2

Compound **16** presents four isomers of configuration due to the chirality of the monospiranes with six-membered rings.[4,5] The flipping of the 1,3-dioxane and cyclohexane rings at r.t. determines the conformational equilibrium of all possible isomers (Scheme 3). The ^{1}H-NMR spectrum of **16** presents two singlets for the 1,3-dioxane ring and for the bromomethyl substituents ($\delta_{3\text{-MeBr}}$=3.58 and $\delta_{4,6}$=3.81

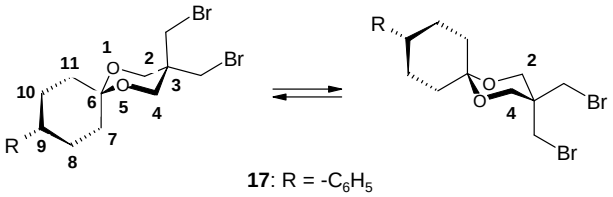
ppm). The ^{1}H-NMR spectrum of **19** shows the same flipping behavior of the 1,3-dioxane and cyclohexane rings, having singlets for cyclohexane ($\delta_{7,8,15,16}$=1.90 ppm) and 1,3-dioxane ($\delta_{2,4,11,13}$= 3.82 ppm) rings protons and bromomethyl substituents ($\delta_{3,12\text{-}MeBr}$=3.60 ppm), respectively.



16

Scheme 3

The monospiranes **17** and **18** present, like **16**, four isomers of configuration due to the chirality of the monospiranes with six-membered rings, with the difference that the carbocycle adopts an anancomeric structure due to the presence of a substituent which prefers the equatorial orientation.[6-8] The 1,3-dioxane rings of **17** and **18** are flexible (Scheme 4), proved by the singlet signals of the bromomethyl substituents [$\delta_{3\text{-}MeBr}$=3.62 ppm (**17**) and 3.59 ppm (**18**)]. The signals of the 1,3-dioxane unit methylens are also singlet, but, due to the anancomeric structure of the cyclohexane ring, the positions 2 and 4 are diastereotopic (*procis* and *protrans*, respectively, referred to the substituent at position 9) and present different chemical shifts [$\Delta\delta$=0.03 ppm (**17**) and 0.05 ppm (**18**)].

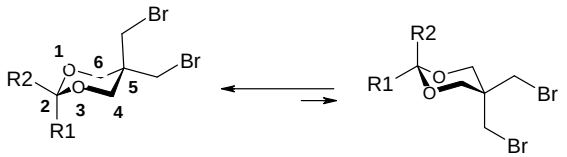


17: R = -C_6H_5
18: R = -CH_3

Scheme 4

In the case of **13**-**15**, **20**, **21** the conformational equilibrium is shifted at r.t. to the isomer in which the more bulky substituent at position 2 lies in the equatorial orientation (Scheme 5). This causes the freezing of the conformational equilibrium

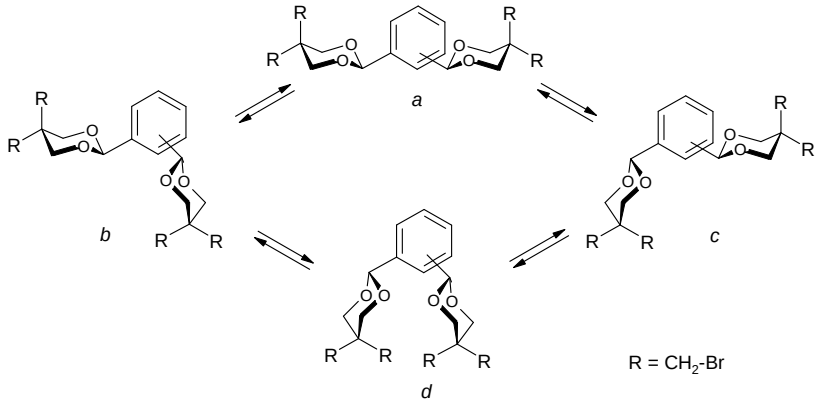
and, consequently, the diastereotopicity of the axial and equatorial protons from positions 4 and 6. The signals of these protons appear in ^{1}H-NMR spectra as an AB system (e.g., $\delta_{4,6\text{-ax.}}$=3.85 ppm, $\delta_{4,6\text{-eq.}}$=4.26 ppm for **13**). Also, the two methylene residues from bromomethyl substituents give in the spectrum two different singlets (e.g., $\delta_{5\text{-MeBr eq.}}$= 3.31 ppm, $\delta_{5\text{-MeBr ax.}}$= 4.00 ppm for **13**).



13: R1 = H, R2 = -C_6H_5
14: R1 = H, R2 = 1-naphthyl
15: R1 = -C_6H_5, R2 = -CH_3

Scheme 5

In **13**, **14**, **20**, **21** the phenyl substituent of the 1,3-dioxane ring adopts, as we have expected, the equatorial conformation. In the case of **20** and **21** there are four conformers due to the free rotation of the 1,3-dioxane rings around the σ bond phenylene-(1,3-dioxane-2-yl) (Scheme 6).



20: o-
21: *m*-

Scheme 6

While for **21** all four conformers *a*-*d* are possible, in the case of **20** the *d* conformer is less probable due to the steric repulsions between the bromomethyl substituents and the unshared pair of electrons of the oxygen atoms, respectively, of the both 1,3-dioxane units. This fact has as result a shift of the acetalic protons signal to lower fields ($\Delta\delta_{H_{2'}}$=0.22 ppm).

Conclusions

The synthesis of a series of 5,5-bis(bromomethyl) 1,3-dioxane derivatives (**12-15**, **20**, **21**) and 1,3-dioxane-based (poly)spiranes (**16**-**19**) was achieved by (a)cetalization of the corresponding carbonyl derivatives with 2,2-bis(bromomethyl)-1,3-propanediol (**11**). Their stereochemistry was discussed using NMR spectra. The study revealed that, depending of the type of substituents on the position 2 of the 1,3-dioxane unit, these compounds have three main conformational behavior: flexible (**12**, **16**, **19**), semi-flexible (**17**, **18**), and anancomeric (**13**-**15**, **20**, **21**).

Experimental

The solvents were purified according to standard procedures[9] and were distilled prior to use. Column chromatography: silica gel 60 (Merck, Darmstadt), mesh 70–230 nm. Thin layer chromatography (TLC): silica gel layered aluminum foil (60 F_{254} Merck, Darmstadt). Melting points (uncorrected) were taken using a Kleinfold APOTEK apparatus. 2,2-bis(bromomethyl)-1,3-propanediol (Aldrich), acetophenone (**4**), 4-phenyl-cyclohexane-one (**6**), 4-methyl-cyclohexane-one (**7**), 1,4-cyclohexane-dione (**8**), ftaldialdehyde (**9**), *iso*-ftaldialdehyde (**10**) were purchased and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded with Varian Gemini 300 and Bruker ARX 300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) or Bruker ARX 200 (200 MHz for ^{1}H and 50 MHz for ^{13}C) using $CDCl_3$ as solvent.

*General procedure for the synthesis of compounds **12-21***

A solution of 10 mmol of 2,2-bis(bromomethyl)-1,3-propanediol (**11**), 10 mmol of the corresponding carbonyl compound (**1**-**10**) and 0.1 g *p*-toluene sulfonic acid in 100 ml benzene was refluxed for two hours. The water was removed using a Dean-Stark trap. After cooling down, the catalyst was neutralized with excess of sodium acetate and the suspension was washed twice with 50 ml water. The organic layer was separated, dried with anhydrous sodium sulfate and the solvent was removed in vacuum. The resulted residue was deposited on silica gel and was purified using column chromatography.

5,5-bis(bromomethyl)-2,2-dimethyl-1,3-dioxane (12)
White solid, m.p. 89-91℃, yield 89%. ^{1}H-RMN (δ, ppm) 1.41 (6H, s), 3.58 (4H, s), 3.80 (4H, s).

5,5-bis(bromomethyl)-2-phenyl-1,3-dioxane (13)
White solid, m.p. 101℃, yield 91%. ^{1}H-RMN (δ, ppm) 3.31 (2H, s), 3.85 (2H, d, ^{2}J=12 Hz), 4.00 (2H, s), 4.26 (2H, d, ^{2}J=12 Hz), 5.41 ppm (1H, s), 7.40-7.44 (2H, m), 7.48-7.51 (2H, m). ^{13}C-RMN (δ, ppm) 34.41 (CH_2), 35.97 (CH_2), 37.30 (C_{quat}), 71.83 (CH_2), 102.21 (CH), 125.98 (CH), 128.30 (CH), 129.20 (CH), 137.22 (C_{quat}).

5,5-bis(bromomethyl)-2-(1'-naphthyl)-1,3-dioxane (14)
White solid, m.p. 128-9℃, yield 3%. ^{1}H-RMN (δ, ppm) 3.36 (2H, s), 4.00 (2H, d, ^{2}J=12 Hz), 4.06 (2H, s), 4.36 (2H, d, ^{2}J=12 Hz), 6.03 (1H, s), 7,56-8,00 (7H, m).

5,5-bis(bromomethyl)-2-methyl-2-phenyl-1,3-dioxane (15)
White solid, m.p. 115℃, yield 90%. ^{1}H-RMN (δ, ppm) 1.56 (3H, s), 3.10 (2H, s), 3.61 (2H, d, ^{2}J=11,74 Hz), 3,88 (2H, d, ^{2}J=11,74 Hz), 4,00 (2H, s), 7,35-7,43 (5H, m). ^{13}C-RMN (δ, ppm) 31.53, 34.67, 36.06, 37.46, 66.07, 76.57, 76.99, 77.42, 101.37, 126.48, 128.12, 128.91, 139.39.

3,3-bis(bromomethyl)-1,5-dioxa-spiro[5.5]undecan (16) White solid, m.p. 79-80°C, yield 85%. ^{1}H-RMN (δ, ppm) 1.38-1.76 ppm (10H, m), 3.58 ppm (4H, s), 3.81ppm, (4H, s); ^{13}C-RMN (δ, ppm) 22.53 (CH_2), 25.60 (CH_2), 32.25 (CH_2), 36.21 (CH_2), 37.31 (C_{quat}), 64.04 (CH_2), 98.90 (C_{quat}).

3,3-bis(bromomethyl)-9-phenyl-1,5-dioxa-spiro[5.5]undecan (17)
White solid, m.p. 125-7°C, yield 80%. ^{1}H-RMN (δ, ppm) 1.46-1.73 (6H, m), 2.31-2.62 (3H, m) 3.62 (4H, s), 3.85 (2H,s), 3.88 (2H, s); 7.18-7.33 ppm (5H, m). ^{13}C-RMN (δ, ppm) 30.12 (CH_2), 32.34 (CH_2), 36.18 (CH_2), 37.99 (C_{quat}), 43.80 (CH), 64.31 (CH_2), 64.45 (CH_2), 98.59 (C_{quat}), 126.9 (CH), 128.43 (CH), 146.38 (C_{quat}).

3,3-bis(bromomethyl)-9-methyl-1,5-dioxa-spiro[5.5]undecan (18)
White solid, m.p. 98-9°C, yield 92%. ^{1}H-RMN (δ, ppm) 0.90 (3H, d, ^{3}J=6.30 Hz), 1.07-1.62 (7H, m), 2.12-2.18 (2H, m), 3.59 (4H, s), 3.78 (2H, s), 3.83 (4H, S); ^{13}C-RMN (δ, ppm) 21.67 (CH_3), 30.74 ppm, (CH_2), 31.87 ppm (CH_2), 31.86 (CH), 36.10 (CH_2), 37.90 (C_{quat}), 64.16 (CH_2), 64.29 (CH_2), 99.01 (C_{quat}).

3,3,12,12-tetrakis(bromomethyl)-1,5,10,14-tetraoxaspiro[5.2.5.2]hexadecan (19)
White solid, m.p. 159-60°C, yield 75%. ^{1}H-RMN (δ, ppm) 1.90 (8H, s), 3.60 (8H, s), 3.82 (8H, s).

1,2-bis[5',5'-bis(bromomethyl)-1',3'-dioxane-2'-yl]-benzene (20)
White solid, m.p.= 135-6, yield 70%. ^{1}H-RMN (δ, ppm) 3.32 (2H, s), 3.86 (2H, d, ^{2}J=11.7 Hz), 4.00 (2H, s), 4.29 (2H, d, ^{2}J=11.7 Hz), 5.65 ppm (2H, s), 7.40-7.43 (2H, m), 7.65-7.68 (2H, m). 34.33 (CH_2), 36.00 (CH_2), 72.18 (CH_2), 100.50 (CH), 115.90 (CH), 119.2 (CH).

1,3-bis[5',5'-bis(bromomethyl)-1',3'-dioxane-2'-yl]-benzene (21)
White solid, m.p.= 142-4°C, yield 76%. ^{1}H-RMN (δ, ppm) 3.33 (2H, s), 3.86 (2H, d, ^{2}J=11.6 Hz), 3.98 (2H, s), 4.27 (2H, d, ^{2}J=11.6 Hz), 5.43 ppm (2H, s), 7.40-7.43 (2H, m), 7.65-7.68 (2H, m). ^{13}C-RMN (δ, ppm) 34.33 (CH_2), 36.00 (CH_2), 72.18 (CH_2), 100.50 (CH), 115.90 (CH), 119.2 (CH).

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