STUDIA UBB. CHEMIA, LV, 3, 2010

SYNTHESIS, STRUCTURE AND REACTIVITY INVESTIGATIONS OF SOME NEW MONO- AND BIS(5,5-DIBROMOMETHYL-1,3-DIOXAN-2-YL) DERIVATIVES

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ABSTRACT. The good yielding synthesis of some new mono and bis(5,5-dibromomethyl-1,3-dioxan-2-yl) derivatives and their NMR structural investigations are reported. Substitution of bromine in bromomethyl groups with thioacetate units in some of these compounds was also investigated.

Keywords: *1,3-dioxanes, dimercapto derivatives, NMR, conformational analysis*

INTRODUCTION

The stereochemistry of saturated six-membered rings were extensively investigated using as model compounds a plethora of differently substituted 1,3-dioxane derivatives [1-5]. The last ones are easily investigated using NMR methods [6], available in good yields by different acetalization reactions [7] and manifest remarkable stability in non-acidic media [8].

In previous works, we investigated either compounds with one, two or even three 1,3-dioxane units connected to the same substrate [9-14] and we found out flexible, semiflexible or anancomeric (rigid) structures. These investigations revealed the high conformation enthalpies (A-values) of the substituents located at position 2 and the preference of these groups for the equatorial orientation [9-14]. If several 1,3-dioxane rings are connected to the same substrate, in the more stable conformation the reference (main) unit occupies similar orientations for all 1,3-dioxane rings. These orientations are similar to those observed in the corresponding mono-1,3-dioxane derivative.

Thus, using the acetalization of 2,2-dibromomethyl-1,3-propanediol with different monocarbonyl and dicarbonyl compounds, we considered of interest to prepare new anancomeric 1,3-dioxanes bearing a “holding group” at position 2 and geminal bromomethyl groups at position 5.

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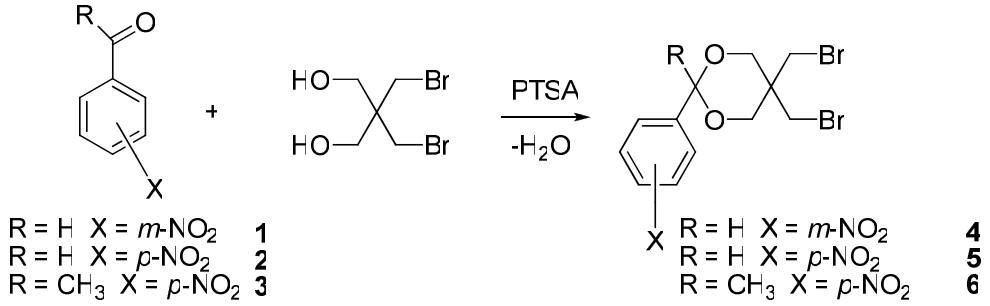
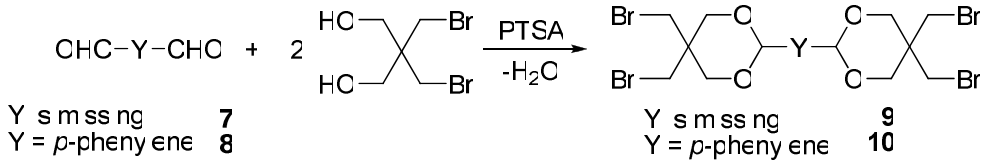
RESULTS AND DISCUSSION

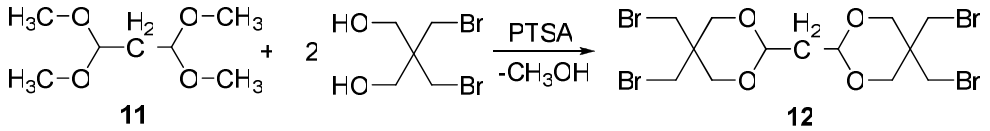
New 1,3-dioxane derivatives (**4**-**6, 9, 10** and **12**) were synthesized in good yields (Table 1) by the acetalization of monocarbonyl derivatives **1**-**3,** dialdehydes **7, 8** and by the transacetalization of 1,1,3,3-tetrametoxipropane **11** with 2,2-dibromomethyl-1,3-propanediol (Schemes 1-3).



Scheme 1



Scheme 2



Scheme 3

Table 1. Results of the syntheses of compounds **4**-**6**, **9**, **10** and **12**

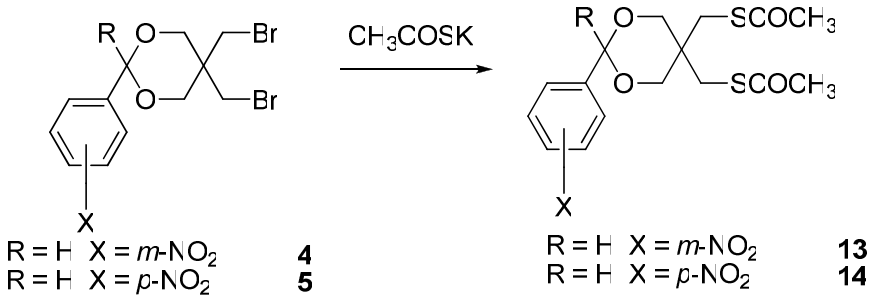
Compd.	**4**	**5**	**6**	**9**	**10**	**12**
Yields (%)	71	83	70	57	64	49

The yields in mono 1,3-dioxane derivatives (**4**-**6**) were higher than those of bis(1,3-dioxan-2-yl) compounds (**9**, **10** and **12**). The yield for the acetalization of *p*-nitrobenzaldehyde (**2**) was higher than that carried out with *p*-nitro-acetophenone **3**.

In order to develop the chemistry of these brominated compounds, we investigated the nucleophilic replacement of the bromine atoms with protected mercapto groups. In this purpose, compounds **4** and **5** were used

as references substrates by applying similar procedures previously described in the literature[15].

Thus, the reaction of **4** and **5** with freshly prepared CH_3COSK in different solvents (CH_2Cl_2, CH_3CN) at room temperature afforded compounds **13** and **14** in poor yields (10-15%, Scheme 4).

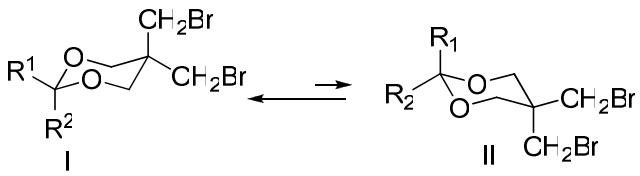


Scheme 4

That is, the raw products were contaminated with important amounts of monomethylthioacetate derivatives and different disulfides as side products.

Compounds **13** and **14** were obtained in good yields by a different approach using as starting material $HOCH_2$-$C(CH_2$-$SCOCH_3)_2$-CH_2OH [16, 17].

All investigated brominated compounds were anancomeric structures as their conformational equilibria (Scheme 5) were shifted towards the conformer (I) in which the larger group (R^1) had an equatorial orientation [R^1 = nitrophenyl (**4** and **5**), CH_3 (**6**), 5,5-dibromomethyl-1,3-dioxan-2-yl (**9**), (*para*-5,5-dibromomethyl-1,3-dioxan-2-yl)phenyl (**10**) and (5,5-dibromomethyl-1,3-dioxan-2-yl)methyl (**12**)].



Scheme 5

The anancomeric behavior of compounds **4**-**6**, **9**, **10** and **12** was deduced from the NMR spectra which exhibit different signals for the axial and equatorial protons of the 1,3-dioxane ring and for the protons and carbon atoms of the axial and equatorial bromomethyl groups located at position 5 (Table 2).

Table 2. Selected NMR data (δ, ppm) for compounds **4-6**, **9**, **10** and **12**

Compd.	^{1}H				^{13}C	
	4-H, 6-H		5-CH_2Br		5-CH_2Br	
	ax	eq	ax	eq	ax	eq
4	3.90	4.29	3.94	3.32	35.7	34.1
5	3.89	4.29	3.94	3.32	35.6	34.1
6	3.52	3.92	3.95	3.11	35.6	34.3
9	3.70	4.20	3.88	3.25	35.5	33.9
10	3.84	4.08	3.96	3.31	36.0	34.4
12	3.62	4.08	3.88	3.23	36.0	34.3

Positions 4 and 6 of the 1,3-dioxane units and the protons of the CH_2Br groups were not diastereotopic. This NMR equivalence, also observed for compound **4** bearing a dissymetrical aromatic group, suggests the free rotation, at room temperature, of the equatorial *meta*-nitrophenyl group group located at position 2.

CONCLUSIONS

New compounds with one or two 1,3-dioxane units were obtained in good yields by acetalization or transacetalization of 2,2-dibromomethyl-1,3-propanediol. The NMR spectra of the new compounds exhibit different signals for the 1,3-dioxanic axial and equatorial protons and for the protons and carbon atoms of the axial and equatorial bromomethyl groups reveal the anancomeric structure of all derivatives. The procedure for the substitution of the bromine atoms of the bromomethyl groups with nucleophiles of type thioacetate was investigated and revealed poor yields for this reaction.

EXPERIMENTAL SECTION

^{1}H NMR (300 or 250 MHz) and ^{13}C NMR (75 or 62.9 MHz) spectra were recorded in $CDCl_3$ on Bruker spectrometers. ESI MS were recorded on Agilent 6320 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.

General procedure for synthesis of derivatives 4-6, 9, 10 and 12

A catalytic amount of *para*-toluenesulfonic acid (PTSA, 0.1 g) was solved in 100 ml toluene. To this solution, 5 (**4**-**6**) or 10 (**9**, **10** and **12**) mmol of 2,2-dibromomethyl-1,3-propanediol and 5 mmol of (di)carbonyl compound or of the tetracetal **11** (synthesis of **12**) were added. The reaction mixture was heated to reflux and the resulting water from the reaction was removed using a Dean-Stark trap (a simple reflux was used in the synthesis of **12**).

When 80% of the theoretical amount of water has been separated (6 - 10 h) the mixture was cooled at room temperature and the PTSA was neutralized with sodium acetate in excess (0.2 g), under stirring (over one hour). The reaction mixture was washed twice with 50 ml water. The organic phase was dried with anhydrous sodium sulphate, and then the toluene was removed in vacuo. The crude solid product was purified by crystallization from ethanol.

5,5-dibromomethyl-2-(3'-nitrophenyl)-1,3-dioxane 4. White solid, m.p. = 79-80 ºC, yield 71%. Calculated for $C_{12}H_{13}Br_2NO_4$ (395.04): C, 36.48; H, 3.32; N, 3.55; Br, 40.45. Found: C, 36.69; H, 3.51; N, 3.43; Br, 40.18. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 3.32 [2H, s, 5-CH_2Br (*eq*)], 3.90 (2H, d, *J* = 12.0 Hz, 4-H_{ax}, 6-H_{ax}), 3.94 [2H, s, 5-CH_2Br (*ax*)], 4.29 (2H, d, *J* = 12.0 Hz, 4-H_{eq}, 6-H_{eq}), 5.49 (H, s, 2-H_{ax}), 7.56 [H, t (overlapped dd), *J*≈*J'*≈8.0 Hz, 5′-H], 7.81 (H, d, *J* = 7.7 Hz, 6′-H), 8.22 (H, d, *J* = 8.2 Hz, 4′-H), 8.34 (H, s, 2′-H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 34.1 [5-CH_2Br(*eq*)], 35.7 [5-CH_2Br(*ax*)], 37.3 (C^5), 71.8 ($C^{4,6}$), 100.3 (C^2), 121.4 ($C^{2'}$), 123.9 ($C^{4'}$), 129.31 ($C^{5'}$), 132.2 ($C^{6'}$), 139.1 ($C^{1'}$), 148.0 ($C^{3'}$).

5,5-dibromomethyl-2-(4'-nitrophenyl)-1,3-dioxane 5. White solid, m.p.= 128-129 ºC, yield 83%. Calculated for $C_{12}H_{13}Br_2NO_4$ (395.04): C, 36.48; H, 3.32; N, 3.55; Br, 40.45. Found: C, 36.33; H, 3.47; N, 3.69; Br, 40.61. ^{1}H NMR (250 MHz, $CDCl_3$, δ ppm): 3.32 [2H, s, 5-CH_2Br (*eq*)], 3.89 (2H, d, *J* = 11.9 Hz, 4-H_{ax}, 6-H_{ax}), 3.94 [2H, s, 5-CH_2Br (*ax*)], 4.29 (2H, d, *J* = 11.9 Hz, 4-H_{eq}, 6-H_{eq}), 5.49 (H, s, 2-H_{ax}), 7.66 (H, d, *J* = 8.7 Hz, 2′,6′-H), 8.24 (H, d, *J* = 8.7 Hz, 3′,5′-H). ^{13}C NMR (62.9 MHz, $CDCl_3$, δ ppm): 34.1 [5-CH_2Br(*eq*)], 35.6 [5-CH_2Br (*ax*)], 37.4 (C^5), 72.0 ($C^{4,6}$), 100.5 (C^2), 123.5 ($C^{3',5'}$), 127.2 ($C^{2',6'}$), 143.6 ($C^{1'}$), 148.3 ($C^{4'}$).

5,5-dibromomethyl-2-methyl-2-(4'-nitrophenyl)-1,3-dioxane 6. White solid, m.p. = 176-177ºC, yield 70 %. Calculated for $C_{13}H_{15}Br_2NO_4$ (409.07): C, 38.17; H, 3.70; N, 3.42; Br, 39.07. Found: C, 38.42; H, 3.51; N, 3.26; Br, 38.89. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.56 (3H, s, 2-CH_3), 3.11 [2H, s, 5-CH_2Br(*eq*)], 3.52 (2H, d, *J*=11.8 Hz, 4-H_{ax}, 6-H_{ax}), 3.92 (2H, d, *J*=11.8 Hz, 4-H_{eq}, 6-H_{eq}), 3.95 [2H, s, 5-CH_2Br (*ax*)], 7.60 (H, d, *J* = 8.9 Hz, 2′,6′-H), 8.27 (H, d, *J* = 8.9 Hz, 3′,5′-H). ^{13}C NMR (62.9 MHz, $CDCl_3$, δ ppm): 30.9 (2-CH_3), 34.3 [5-CH_2Br (*eq*)], 35.6 [5-CH_2Br (*ax*)], 37.5 (C^5), 66.3 ($C^{4,6}$), 100.7 (C^2), 124.3 ppm ($C^{3'}$,$C^{5'}$), 127.6 ($C^{2'}$,$C^{6'}$), 147.2 ($C^{1'}$), 148.0 ($C^{4'}$).

bi(5,5-dibromomethyl-1,3-dioxan-2-yl) 9. White solid, m.p. = 199.2ºC, yield 57 %. Calculated for $C_{12}H_{18}Br_4O_4$ (545.88): C, 26.40; H ,3.32; Br, 58.55. Found: C, 26.58; H ,3.44; Br, 58.32. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 3.25 [4H, s, 5(5')-CH_2Br (*eq*), 3.70 [4H, d, *J* = 11.8 Hz, 4(4')-H_{ax}, 6(6')-H_{ax}), 3.88 (4H, s, 5(5')-CH_2Br (*ax*)], 4.20 [4H, d, *J* = 11.8 Hz, 4(4')-H_{eq}, 6(6')-H_{eq}], 4.43 (H, s, 2-H_{ax}). ^{13}C NMR (62.9 MHz, $CDCl_3$, δ ppm): 33.9 [5-CH_2Br (*eq*)], 35.5 [5-CH_2Br (*ax*)], 37.7 (C^5), 71.5 ($C^{4,6}$), 100.0 (C^2).

1,4-Bis(5',5'-dibromomethyl)-1',3'-dioxan-2'-yl)benzene 10. White solid, m.p.=204-205ºC, yield 64%. Calculated for $C_{18}H_{22}Br_4O_4$ (621.98): C, 34.76; H, 3.57; Br, 51.39. Found: C, 34.92; H, 3.40; Br, 51.25. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 3.31 [4H, s, 5'(5")-CH_2Br (*eq*)], 3.84 [4H, d, *J* = 10.8 Hz, 4'(4")-H_{ax}, 6'(6")-H_{ax}], 3.96 (4H, s, 5(5')-CH_2Br(*ax*)], 4.24 [4H, d, *J* = 10.8 Hz, 4'(4")-H_{eq}, 6'(6")-H_{eq}], 5.41 [2H, s, 2'(2")-H], 7.49 (4H, s, 2-H, 3-H, 5-H, 6-H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 34.4 [5'(5")-CH_2Br(*eq*)], 36.0 [5'(5")-CH_2Br(*ax*)], 37.4 ($C^{5',5"}$), 71.8 ($C^{4',4",6',6"}$), 101.8 ($C^{2',2"}$), 126.0 ($C^{2,3,5,6}$), 138.2 ($C^{1,4}$).

Bis(5,5-dibromomethyl-1,3-dioxan-2-yl)methane 12. White solid, m.p.= 151.5 ºC, yield 49%. Calculated for $C_{13}H_{20}Br_4O_4$ (559.91): C, 27.89; H, 3.60; Br, 57.08. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.03 (2H, t, *J* = 5.5 Hz, 2(2')-CH_2-), 3.23 [4H, s, 5(5')-CH_2Br (*eq*)], 3.62 (4H, d, *J* = 11.8 Hz, 4(4')-H_{ax}, 6(6')-H_{ax}), 3.88 [4H, s, 5(5')-CH_2Br (*ax*)], 4.08 (4H, d, *J* = 11.8 Hz, 4(4')-H_{eq}, 6(6')-H_{eq}], 4.59 [2H, t, *J* = 5.4 Hz, 2(2')-H_{ax}]. ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 34.3 [5(5')-CH_2Br (*eq*)], 36.0 [5(5')-CH_2Br (*ax*)], 37.3 ($C^{5,5'}$), 39.5 (CH_2), 71.4 ($C^{4,4',6,6'}$), 99.6 ($C^{2,2'}$).

ACKNOWLEDGMENTS

We acknowledge the financial support of this work by PNCDI II program (UEFISCSU; projects IDEAS 515, 2278).

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