

*Dedicated to Professor Victor-Emanuel Sahini
on the occasion of his 80th anniversary*

SYNTHESIS OF BENZYLIDENE ACETALS OF N-ACETYL-N-METHYL GLUCAMINE

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Received October 24, 2006

Acetalization of N-acetyl-N-methyl-1-amino-1-deoxy-D-glucitol with 2.5 equivalents of 1,1-dimethoxybenzaldehyde in N,N-dimethylformamide at reflux temperature with camphorsulphonic acid as catalyst yielded 5,6-O-benzylidene-N-acetyl-N-methyl-glucamine as the major product. 2,3:4,6-di-O-benzylidene-N-acetyl-N-methyl-glucamine, 4,6-O-benzylidene-N-acetyl-N-methyl-glucamine and a mixture of 2,3:5,6- and 3,4:5,6-di-O-benzylidene-N-acetyl-N-methyl-glucamine have also been isolated as byproducts. Separation and purification conditions of these new products are described. The structures have been assigned by ¹³C-NMR and MS-EI.

INTRODUCTION

The development of new biocompatible and biodegradable surfactants based on natural feedstocks is subject of an increasing scientific and industrial interest.¹ In the last 20 years, aminoalditol derivatives were investigated for their properties as surfactants as well as pseudoceramides.^{2,3} The use of N-methyl-glucamine (an accessible and cheap aminoalditol) allows two strategies in order to obtain a compound with amphipatic character that could exhibit ceramide properties: a) attachment of a nonpolar tail to the amine function followed by the attachment of a second nonpolar tail to the alcohol function; b) creation of an amide bond at the amine function (by acylation) followed by the attachment of two nonpolar tails at the alcohol functions.

These two options can be realized with biocatalysts, using the catalytic capacity and the specificity of lipases.^{4,5} A new approach in the synthesis of these compounds starts from N-acetyl-N-methyl glucamine and consists in the enzymatic attachment of fatty acids by esterification or transesterification reactions catalyzed by lipases.⁶ The reaction monitorization can easily be

performed by HPLC or GC, whether mono- and diesters of N-acetyl-N-methyl-glucamine are available as standard compounds. The selective esterification of each alcohol function in the aminoalditol requires acetal derivatives as intermediates. This paper presents the results of acetalization of N-acetyl-N-methyl-1-amino-1-deoxy-D-glucitol with dimethoxy benzaldehyde in acid catalysis.

RESULTS AND DISCUSSION

The condensation of aldehydes and ketones with alcohols is one of the first reactions studied in organic chemistry. E. Fischer obtained in 1895 for the first time, fructose acetals and then glucose acetals, in acid catalysis.⁷ Acetals can be obtained in acidic, basic or neutral conditions or using other methods.⁸ A series of well documented reviews present results of the acetalization reaction for alditols,⁹ aldoses, aldosesides,^{10,11} and ketoses,¹² but not of aminoalditols.

The acetalization of N-acetyl-N-methyl-glucamine was performed by transacetalization reaction in acidic media using dimethoxy

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benzaldehyde (see the experimental part). The reaction was monitored by TLC and the inspection of the plate showed 5 spots at the following R_f values: spot 1 (0.74), spot 2 (0.67), spot 3 (0.55), spot 4 (0.24) and spot 5 (0.15) (AcOEt:MeOH = 90:10) (Figure 1).

Considering the TLC plate polarity and the eluent polarity we used, the spots on the TLC plate (Figure 1) can be assigned as follows: spots 1, 2 and 3 for di-benzylidene derivatives and spots 4 and 5 for mono-benzylidene derivatives.

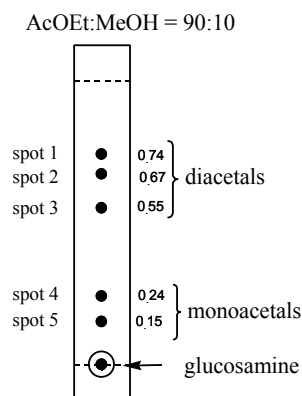


Fig. 1 – TLC analysis of reaction mixture.

After separation by flash chromatography, the compounds have been analyzed by MS-EI. Spots 1, 2 and 3 are di-benzylidene derivatives and have the molecular peak at $m/z = 413(M^+)$ for a 22 eV ionization energy, thus confirming the proposed assignments. Spot 1 was characterized as acetylated derivative, having the molecular peak at $m/z = 455(M^+)$, 24 eV.

The analysis of ¹H-NMR spectra is difficult because the 8 protons in the linear side chain are localized in the 3.5-4.3 ppm interval and the coexistence of *cis-trans* conformers of the amide bond (Figure 2) determines the doubling of the total number of signals.

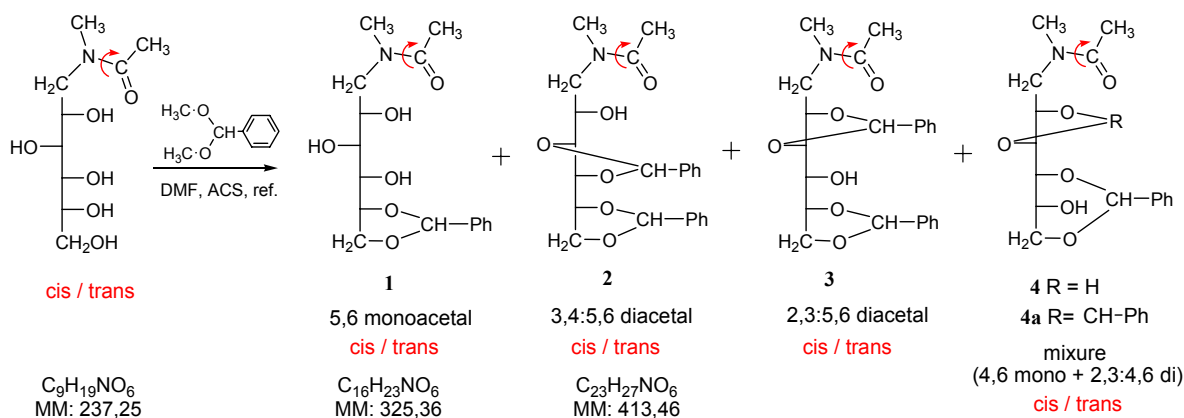


Fig. 3 – Mono- and diacetals as reaction products.

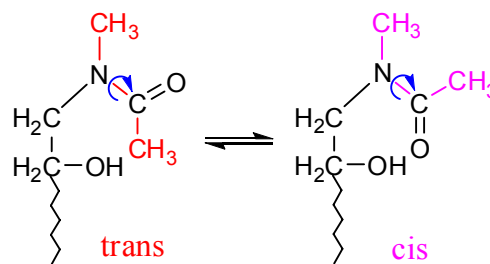


Fig. 2 – *cis-trans* conformers of N-acetyl-N-methyl-glucosamine and derivatives.

The ¹³C-NMR spectroscopy offers valuable data concerning the nature of the acetal rings as well as their positions.^{13,14} Buchanan and coworkers,^{15,16} observed that the chemical shift of the acetal carbon atom is strongly influenced by the size of the ring and is situated in the following intervals:

108.1-115.7 ppm for 1,3-dioxolane rings

97.1-101.1 ppm for 1,3-dioxane rings

100.8-102.3 ppm for 1,3-dioxepane rings

The ¹³C-NMR spectra analysis of spot 1 shows 8 signals in the 169.4 - 171.2 ppm interval, which indicate the existence of 2 isomers, each one with 2 conformers. The 4 signals situated in the 103.7 - 104.2 ppm interval correspond to 4 acetalic C atoms from 1,3-dioxolanic rings and belong to 2 dibenzylidene isomers, both with 2 conformers. These chemical shifts are deshielded (they are present at lower ppm values: 103.7 - 104.2 ppm) comparing with literature data (108.1 - 115.7 ppm for 3-dioxolanic rings,^{15,16}) because of the influence of Ph. Hereby the 2 isomers from spot 1 can only be the compounds **2** and **3** from Figure 3: 2,3:5,6-di-O-benzylidene-N-acetyl-N-methyl-glucosamine and 3,4:5,6-di-O-benzylidene-N-acetyl-N-methyl-glucosamine. Assigning position 5,6 to one of the benzylidene groups will be explained below.

^{13}C -NMR spectra analysis of spot 2 reveals 4 signals: at 103.7 and 104.5 ppm the signals correspond to an acetalic C from 1,3-dioxolane ring (the signals are shifted to a higher value of the magnetic field because of the influence of the phenyl group (Ph) comparing with the literature data^{15, 16}), and at 100.7 and 101.0 ppm the signals correspond to an acetalic C from 1,3-dioxane ring.

Admitting that the initial and kinetically more stable 5, 6-benzylidene derivative is stabilized in time to the thermodynamically more stable 4,6-benzylidene isomer, results that spot 2 can be assigned solely to compound **4a** (Figure 3) namely 2,3:4,6-di-O-benzylidene-N-acetyl-N-methyl-glucamine. The 3,5:4,6 and 2,5:4,6 isomers are excluded because the chemical shifts of acetalic C at 105.0 and 104.1 ppm are clearly assigned to a dioxolanic ring.

Although isopropylidene and cyclohexylidene aminoalditol acetals have already been described,^{20,21} there are no data about benzylidene acetals, consequently the position of benzylidene group had to be established. The analysis of ^1H -NMR spectra is difficult and does not give any valuable information. To spread the hydrogen atom attached on carbon atom with free hydroxyl groups from compound of spot 4, the free hydroxyl groups were derivatized by acetylation and then analysed by ^1H -NMR.

The type of ring was deduced from chemical shifts of the acetalic C atom from the ^{13}C -NMR spectra. There are 2 signals at 103.5 ppm and 103.9 ppm which indicate a 1,3-dioxolane ring and thereby the spot 4 corresponds to compound **1** (Figure 3): 5,6-O-benzylidene-N-acetyl-N-methyl-glucamine. The position of the 1,3-dioxolane ring on the linear side chain was determined by NMR experiments: monodimensional APT and bidimensional COSY and HETCOR. The assignment of C atoms from the linear side chain was established by HETCOR and APT experiments only for C1 and C6.

The presence of *cis-trans* conformers (Figure 2) was proven previously by our group.^{20,21} Obtaining mainly 5,6-O-acetals of N-acetyl-N-methyl-glucamine is in agreement with the literature concerning kinetic acetalization of diethyl-dithioacetals of glucose, galactose and arabinose,¹⁷⁻¹⁹ and for isopropylidene and cyclohexylidene acetals of N-acetyl-N-methyl-glucosamine.^{20,21}

The ^{13}C -NMR spectra analysis of spot 5 reveals the existence of 1,3-dioxane ring (100.4 and 100.5 ppm) and it was assigned to compound **4** from Figure 3 (4, 6-benzylidene isomer of N-acetyl-N-methyl-glucamine). The benzylation of compound **1** (spot 4) (NaH, BnBr) followed by hydrolysis of the benzylidene acetal (I_2/MeOH) leads finally to 2,3,4-tri-O-benzyl-N-acetyl-N-methyl-glucosamine. This compound was also obtained from 5,6-isopropylidene-N-acetyl-N-methyl-glucosamine,²¹ and from 5,6-cyclohexylidene-N-acetyl-N-methyl-glucosamine²², their structures were previously established.²¹ These compounds were obtained by the same reaction path, the obtained compounds presenting identical IR spectra. Therefore the assigned structure of compound **4** (spot 5) was also confirmed by a chemical way.

The procedure and the complete description of the ^{13}C -NMR spectra are presented in the experimental part. The description of structures was done for both conformers together and the notation used is: (*cis, trans*) (Figure 2), meaning that both signals are present and also that the number of signals is double.

EXPERIMENTAL

Equipment:

NMR spectra were recorded on a Varian Gemini 300 MHz apparatus against the line of the solvent (CDCl_3). Chemical shifts are expressed in ppm. Mass spectra were recorded on a Varian Finnigan Mat 212 mass spectrometer. TLC analysis was performed on Kieselgel Merck plates with fluorescence indicator. Separation by flash chromatography was performed on 220-400 mesh silica (Aldrich). Visualization of the chromatograms was accomplished with a UV lamp and by developing with a 20% H_2SO_4 in ethanol solution, then heating the plate at 120 °C. Anhydrous solvents were used.

General Method:

2 g (8.4 mmol) N-acetyl-N-methyl-glucamine is solved in 5 ml DMF (kept on 4Å molecular sieves) and a catalytic amount of camphorsulphonic acid is added under stirring. The reaction mixture is cooled to 0 °C and 3.6 ml (24 mmol) dimethoxy benzaldehyde are added drop-wise under argon atmosphere and stirring. The reaction mixture is stirred at reflux temperature (48 h) until TLC control (Figure 1) ($\text{AcOEt}:\text{MeOH} = 90:10$) indicates the disappearance of the starting material. The reaction is stopped by adding 0.5 ml Et_3N and the solvents are vacuum distilled with toluene. The mixture is then separated and purified by flash chromatography (Table 1).

The 5,6-O-benzylidene-N-acetyl-N-methyl glucosamine was obtained in 52% yield. All products are consistent clays at room temperature.

Table 1

Flash chromatography and TLC separation and analysis conditions of the acetalization products

Spots separation	FC elution system	TLC control system
1+2+3 spots by 4+5 spots	Tol:AcOEt=22:78	AcOEt :MeOH=90:10
1+2 spots by spot 3	Tol:AcOEt=22:78	AcOEt :MeOH=90:10
spot 1 by spot 2	Tol:AcOEt=22:78	AcOEt :MeOH=90:10
spot 3 by spot 2	Tol:AcOEt=25:75	AcOEt :MeOH=95:5
spot 4 by spot 5	Tol:AcOEt=25:75	AcOEt :MeOH=95:5
spot 5 by 4+5 spots	Tol:AcOEt=25:75	AcOEt :MeOH=95:5

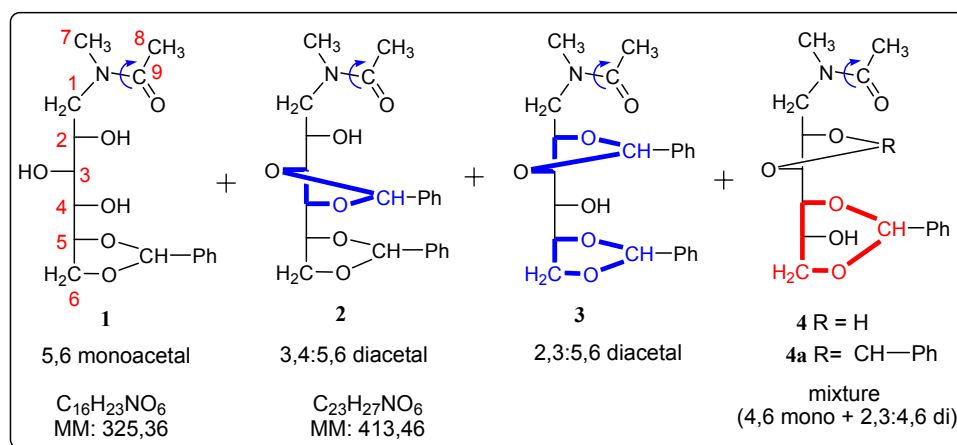


Fig. 3a – (dioxolane ring: 5 atoms ; dioxane ring: 6 atoms).

Spot 1 (C₂₃H₂₇NO₆), (mixture of compounds **2** and **3**, Figure 3a): 2,3:5,6-*O*-benzylidene-*N*-acetyl-*N*-methyl-glucosamine (**2**) + 3,4:5,6-*di-O*-benzylidene-*N*-acetyl-*N*-methyl-glucosamine (**3**)

TLC: R_f = 0.74 (AcOEt:MeOH = 90:10)

MS(ED), 22eV, (C₂₃H₂₇NO₆) m/z = 413(M⁺)

¹H-RMN (300MHz, CDCl₃): δ_H

7.33-7.51 (20H, m, 5xCH from Ph1, 5xCH from Ph2, the isomers 2+3, (*cis*, *trans*)),

5.88-6.00 (4H, m, O-CH-Ph1 and O-CH-Ph2, the isomers 2+3, (*cis*, *trans*))

4.51-3.27 (12H, m, H₂, H₃, H₄, H₅, C(6)H₂, the isomers 2+3, (*cis*, *trans*))

3.07-2.90 (10H, m, N-CH₃, N-C(1)H₂-C2, the isomers 2+3, (*cis*, *trans*))

2.71, 2.75 (2H, 2s, C(3)-OH from the isomer 2, C(4)-OH from the isomer 3, (*cis*, *trans*))

2.09-1.94 (6H, m, N-COCH₃, the isomers 2+3, (*cis*, *trans*))

¹³C-RMN (75MHz, CDCl₃): δ_C:

170.86, 171.27, 171.34, 171.38 (2C, N-C=O, (the isomers 2+3), (*cis*, *trans*))

136.45-137.91 (multiple signals) (4C, 2x C from Ph, (the isomers 2+3), (*cis*, *trans*))

129.50-126.23 (multiple signals) (20C, 10x CH from Ph, (the isomers 2+3), (*cis*, *trans*))

102-92-104.52 (multiple signals) (4C, 2x CH-Ph, (the isomers 2+3), (*cis*, *trans*))

76.18-80.36 (multiple signals) (7C, C₂, C₃, C₅, (the isomers 2+3), (*cis*, *trans*), C₄-OH from the isomer 3, (*cis*, *trans*))

70.68, 70.94 (1C, C₂-OH from the isomer 2, (*cis*, *trans*))

68.63, 68.33, 68.22, 67.69 (2C, C₆, (the isomers 2+3), (*cis*, *trans*))

48.41, 48.54, 48.95, 49.07 (2C, C₁, (the isomers 2+3), (*cis*, *trans*))

37.11, 37.57, 37.81, 37.95 (2C, CH₃-N, (the isomers 2+3), (*cis*, *trans*))

21.21, 21.26, 21.51, 21.61 (2C, N-COCH₃, (the isomers 2+3), (*cis*, *trans*))

Obs: each of the C and H atoms of the two isomers (2 and 3 in Figure 3) has a double number of signals due to the presence of the *cis-trans* isomers.

Spot 2 (C₂₃H₂₇NO₆) (compound **4a** from Figure 3a): 2, 3 :4, 6-*di-O*-benzylidene-*N*-acetyl-*N*-methyl-glucosamine

TLC: R_f = 0.67 (AcOEt:MeOH = 90:10)

MS(ED), 22eV, (C₂₃H₂₇NO₆), m/z = 413(M⁺)

¹H-RMN (300MHz, CDCl₃): δ_H

7.36-7.50 (10H, m, 5xCH from Ph1, 5xCH from Ph2, (*cis*, *trans*)),

5.61-6.08 (2H, m, O-CH-Ph1 and O-CH-Ph2, (*cis*, *trans*))

3.39-4.51 (8H, m, H_{1a}, H_{1b}, H₂, H₃, H₄, H₅, H_{6a}, H_{6b}, (*cis*, *trans*))

3.08, 3.09 (3H, s, N-CH₃, (*cis*, *trans*))

2.92, 2.95 (1H, s, C(5)-OH, (*cis*, *trans*))

2.06, 2.07 (3H, m, N-COCH₃, (*cis*, *trans*))

¹³C-RMN (75MHz, CDCl₃)

171.97, 171.46, (1C, N-C=O, (*cis*, *trans*))

137.97, 137.50, (2C, C from Ph, (*cis*, *trans*))

129.61, 129.57, 129.41, 129.35, 129.09, 128.99, 128.38,

128.28, 128.27, 128.17, 126.71, 126.61, 126.55, 126.43,

126.34, 125.92, (10C, CH from Ph, (*cis*, *trans*))

104.52, 104.33, 103.70, (1C, CH-Ph, (*cis*, *trans*)), from dioxolane ring

101.02, 100.90, 100.76, (1C, CH-Ph, (*cis*, *trans*)), from dioxane ring

78.69-68.56 (multiple signals), (4C, C₂, C₃, C₄, C₅, (*cis*, *trans*))

67.91, 67.55, (1C, C₆, (*cis*, *trans*))

49.02, 48.91, (1C, C₁, (*cis*, *trans*))

38.42, 38.16, (1C, N-CH₃, (*cis*, *trans*))

21.75, 21.63, (1C, COCH₃, (*cis*, *trans*))

Spot 3 (C₂₃H₂₇NO₆): mixture of *di-O*-benzylidene derivatives. Possible to be rearrangement isomers

TLC: $R_f = 0.55$ (AcOEt:MeOH = 90:10)
MS(EI), (22eV), ($C_{23}H_{27}NO_6$), $m/z = 413$ (M^+)

Spot 4 ($C_{16}H_{23}NO_6$) (compound **1** from Figure 3a): 5,6-*O*-benzylidene-*N*-acetyl-*N*-methyl-glucosamine

MS(EI), (24eV) ($C_{16}H_{23}NO_6$), $m/z = 325$, (M^+)

TLC: $R_f = 0.24$ (AcOEt:MeOH = 90:10)

¹H-RMN (300MHz, CDCl₃): δ_H

7.35, 7.36, 7.43, 7.44, 7.45 (5H, m, $\underline{5xCH}$ from Ph, (*cis*, *trans*))

5.76, 5.89 (1H, 2s, O- \underline{CH} -Ph, (*cis*, *trans*))

3.48-3.56 (2H, 2dd, $\underline{H1_a}$, $\underline{H1_b}$, (*cis*, *trans*))

4.24-4.29 (2H, m, $\underline{H6_a}$, $\underline{H6_b}$, (*cis*, *trans*))

3.59-4.31 (4H, m, $\underline{H2}$, $\underline{H3}$, $\underline{H4}$, $\underline{H5}$, (*cis*, *trans*))

3.02, 3.08 (3H, 2s, N- $\underline{CH_3}$, (*cis*, *trans*))

2.11, 2.09 (3H, 2s, N-CO $\underline{CH_3}$, (*cis*, *trans*))

unassigned (3H, m, $3xCH-OH$, (*cis*, *trans*))

¹³C-RMN (75MHz, CDCl₃)

173.06, (1C, N- $\underline{C=O}$, (*cis*, *trans*))

137.87, 137.29, (1C, \underline{C} from Ph, (*cis*, *trans*))

129.28, 129.13, 128.26, 128.19, 126.54, 126.44, 126.33,

126.31, 126.03, (5C, \underline{CH} from Ph, (*cis*, *trans*))

103.98, 103.57, (1C, \underline{CH} -Ph, (*cis*, *trans*))

74.02, 73.60, 72.47, 72.43, 70.09, 69.74, 69.67, 68.17, (4C,

$\underline{C2}$, $\underline{C3}$, $\underline{C4}$, $\underline{C5}$, (*cis*, *trans*))

68.17, (1C, $\underline{C6}$, (*cis*, *trans*))

51.63, (1C, $\underline{C1}$, (*cis*, *trans*))

38.01, 37.95, (1C, $\underline{CH_3}$ -N, (*cis*, *trans*))

21.63, 21.58, (1C, $\underline{CH_3}$ -CO, (*cis*, *trans*))

Spot 5 ($C_{16}H_{23}NO_6$), (compound **4** from Figure 3a): 4,6-*O*-benzylidene-*N*-acetyl-*N*-methyl-glucosamine

TLC: $R_f = 0.15$ (AcOEt:MeOH = 90:10)

MS(EI), (24eV) ($C_{16}H_{23}NO_6$), $m/z = 325$, (M^+)

¹H-RMN (300MHz, CDCl₃): δ_H

7.45-30 (5H, m, $\underline{5xCH}$ from Ph, (*cis*, *trans*))

5.92, 5.88 (1H, 2s, O- \underline{CH} -Ph, (*cis*, *trans*))

3.76-4.44 (8H, m, $\underline{H1_a}$, $\underline{H1_b}$, $\underline{H2}$, $\underline{H3}$, $\underline{H4}$, $\underline{H5}$, $\underline{H6_a}$, $\underline{H6_b}$, (*cis*, *trans*))

4.32-4.20 (3H, m, $3xCH-OH$, (*cis*, *trans*))

3.10, 3.05 (3H, 2s, N- $\underline{CH_3}$, (*cis*, *trans*))

2.05, 2.03 (3H, 2s, N-CO $\underline{CH_3}$, (*cis*, *trans*))

¹³C-RMN (75MHz, CDCl₃)

172.18, (1C, N- $\underline{C=O}$, (*cis*, *trans*))

137.73, 137.33, (1C, \underline{C} from Ph, (*cis*, *trans*))

128.38, 128.27, 128.20, 126.75, 126.67, 126.56, 126.42,

126.23, 125.97, (5C, \underline{CH} from Ph, (*cis*, *trans*))

100.59, 100.47, (1C, \underline{CH} -Ph, (*cis*, *trans*))

79.53, 79.09, 78.40, 78.34, 78.04, 72.38, 72.24, 70.13, 69.57,

69.30, 62.71 (4C, $\underline{C2}$, $\underline{C3}$, $\underline{C4}$, $\underline{C5}$, (*cis*, *trans*))

63.44, (1C, $\underline{C6}$, (*cis*, *trans*))

49.50, 49.11, (1C, $\underline{C1}$, (*cis*, *trans*))

38.47, 38.41, (1C, N- $\underline{CH_3}$, (*cis*, *trans*))

21.72, 21.59, (1C, N-CO $\underline{CH_3}$, (*cis*, *trans*))

Obs: The number of C and H atoms in the description of the ¹³C-RMN spectra refers only to one of the respective isomers (or of the mixture of isomers 2 and 3). The atoms corresponding to the *cis-trans* isomerisation are emphasized only for one of them, their number being double than the one specified in the description.

Acknowledgements: The authors thank Dr. Miron Teodor Căprioiu ("C. D. Nenițescu" Organic Chemistry Center, Bucharest, Roumania) for ¹H-NMR and ¹³C-NMR analyses, and to Valentin Badea ("Politehnica" University, Faculty of Industrial Chemistry and Environmental Engineering, Timișoara, Roumania) for mass spectroscopy analyses. We

also thank Dr. Francisc Peter ("Politehnica" University, Faculty of Industrial Chemistry and Environmental Engineering, Timișoara, Roumania) for providing us the *N*-acetyl-*N*-methyl-glucosamine and to Dr. Eugen Sîșu (Victor Babeș" University of Medicine and Pharmacy, Department of Biochemistry) for his helpful advice in performing the syntheses.

CONCLUSIONS

The reaction between *N*-acetyl-*N*-methyl-glucosamine and dimethoxy benzaldehyde in acid catalysis (camphorsulphonic acid) gives mainly the 5,6-monobenzylidene acetal (compound **1**, Figure 3) with 52% yield. The new compounds: 5,6-*O*-benzylidene-*N*-acetyl-*N*-methyl-glucosamin (as main product), 2,3:4,6-di-*O*-benzylidene-*N*-acetyl-*N*-methyl-glucosamine, 4,6-*O*-benzylidene-*N*-acetyl-*N*-methyl-glucosamine and a mixture of 2,3:5,6- with 3,4:5,6-di-*O*-benzylidene-*N*-acetyl-*N*-methyl-glucosamine (not previously described in literature), were characterized by MS-EI, ¹H-NMR, and ¹³C-NMR. The identity of the products was confirmed by MS and the ring type was established by ¹³C-NMR, COSY and HETCOR experiments. The careful study of the spectra indicates the existence of *cis-trans* conformers (Figure 2). The existence of conformers makes their characterization by ¹H-NMR difficult, therefore they were characterized mainly by ¹³C-RMN. The optimal conditions for reaction monitorization and for flash chromatography separation and purification have also been established.

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