Chemistry of Natural Compounds, Vol. 45, No. 4, 2009

SYNTHESIS OF SOME 1,2-*trans*-GLUCOSIDES CONTAINING DIBENZOOXABICYCLOAMINES

N. N. Sidamonidze, R. O. Vardiashvili,*
M. I. Gverdtsiteli, and R. A. Gakhokidze

UDC 577.1

*Condensation of 1-chloro-2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose with dibenzooxabicycloamine derivatives in the presence of freshly prepared Ag_2CO_3 catalyst was studied for the first time. New 1,2-*trans*-glycosides containing dibenzooxabicycloamines were prepared.*

Key words: dibenzooxabicycloamine derivatives, Ag_2CO_3, 1,2-*trans*-glucosides.

Little has been published about carbohydrates containing heterocyclic compounds. However, such compounds are definitely of practical interest for synthesizing new types of 1,2-*trans*-glucosides [1–3].

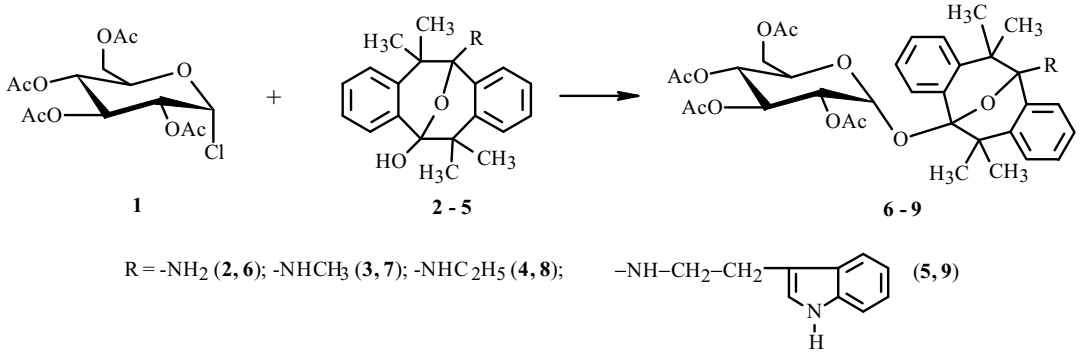
We propose a convenient method for synthesizing new types of heterocyclic derivatives of 1,2-*trans*-glucosides.

Condensation of 1-chloro-2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose (**1**) with 4,4,8,8-tetramethyl-2,3,6,7-dibenzo-9-oxabicyclo-(3,3,1)-nonan-1-*N*-amino-5-ol (**2**); 4,4,8,8-tetramethyl-2,3,6,7-dibenzo-9-oxabicyclo-(3,3,1)-nonan-1-*N*-methylamino-5-ol (**3**); 4,4,8,8-tetramethyl-2,3,6,7-dibenzo-9-oxabicyclo-(3,3,1)-nonan-1-*N*-ethylamino-5-ol (**4**); and 4,4,8,8-tetramethyl-2,3,6,7-dibenzo-9-oxabicyclo-(3,3,1)-nonan-1-*N*-tryptamin-5-ol (**5**) at room temperature in the presence of freshly prepared Ag_2CO_3 catalyst in ether solution produced **6**–**9**, respectively, according to Scheme 1.

The course of reactions was monitored by TLC. The reactions took 14-16 h to produce mainly 1,2-*trans*-glycosides **6**–**9** although small quantities of the 1,2-*cis*-isomers were also observed. The products were yellow crystalline compounds that were soluble in $CHCl_3$ and alcohol (MeOH, EtOH). The yields of **2**–**5** decreased as the radical bonded to the heterocycle increased. This was probably due to steric factors.

These are nucleophilic substitution reactions that occur through an S_N2 mechanismm. The direction of the reaction depends on the relative configuration of C_1 and C_2 in the starting acylated chloroglucose and on the acceptor of the released HCl. Condensation of 1,2-*cis*-acylglycosylhalides with alcohols in the presence of Ag_2CO_3 occurred mainly with C_1 configuration inversion, resulting in formation of 1,2-*trans*-glycosides [4].

We performed quantum-chemical calculations using CS Mopac2000 Version 1.11 in order to justify theoretically the direction of the condensation of 1-chloro-2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose with the dibenzooxabicycloamine derivatives. Compounds were optimized before each AM1 (Austin Model 1) calculation by minimizing the energy using molecular mechanics (MM) and quantum-chemical methods [5].

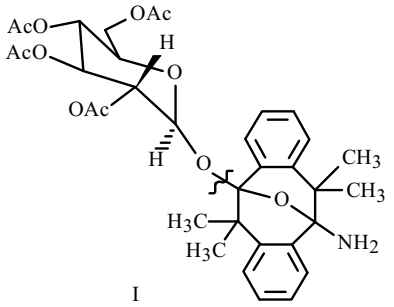


Scheme 1

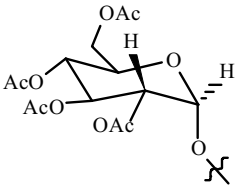
Dzhavakhishvili Tbilisi State University, Georgia, 0128, prosp. I. Chavchavadze, 3, e-mail: exo@tsu.ge. Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 422–424, July–August, 2009. Original article submitted March 9, 2009.

 0009-3130/09/4504-0496 ©2009 Springer Science+Business Media, Inc.

The model condensation was the reaction of 1-chloro-2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose (**1**) with 4,4,8,8-tetramethyl-2,3,6,7-dibenzo-9-oxabicyclo-(3,3,1)-nonan-1-*N*-amino-5-ol (**2**). Two possible reaction pathways were examined that formed the 1,2-*trans*-glucoside (structure I) and the 1,2-*cis*-glucoside (structure II).



I



II

The calculated heats of formation of the products showed that the probability of generating structure I was greatest, $\Delta H_f = -1095.39$ kJ/mol (structure II, $\Delta H_f = -1087.68$ kJ/mol). This was confirmed by PMR spectroscopy. PMR spectra of **6**–**9** showed resonances of anomeric proton H-1 bonded to C-1 at δ 4.43–4.52 and splitting as a result of coupling with H atoms on C-2 into two lines with SSCC $J_{1,2} = 8.0$ Hz. This value was typical of axial–axial placement of the coupled atoms (1,2-*trans*-glycoside).

Unique mathematical formulations, topological indices (molecular descriptors), allow structure–property correlation equations to be constructed and studied for various classes of chemical compounds [6, 7].

The logarithm of the determinant of the quasi-PNS-matrix ($P\tilde{N}S$) is an effective topological index. It was used to study theoretically several dozen classes of organic compounds [8, 9].

The diagonal elements of the $P\tilde{N}S$. matrix are sums of the serial numbers of the chemical elements included in the individual structural fragments of the molecule; off-diagonal elements, the multiplicity of chemical bonds between structural fragments.

A simple model was developed for **6**–**9**:

where X denotes a $C_{34}H_{41}O_{11}N$ fragment; Y, H; and V = H (**6**), CH_3 (**7**), C_2H_5 (**8**), and 2-(3-indolyl)ethyl (**9**).

The corresponding $P\tilde{N}S$ matrix has the form

$$\begin{Vmatrix} Z_X & 1 & 1 \\ 1 & Z_Y & 0 \\ 1 & 0 & Z_V \end{Vmatrix}$$

where Zx is the sum of the serial number of the chemical elements in the X fragment; Zy, in Y; Zv, in V; the number "1", the multiplicity of the bond between X and Y (X and V).

The following correlation equation was constructed:

$$T_m = 36.61g(\Delta P\tilde{N}S) + 18.7$$

The calculations showed that the correlation coefficient r was 0.988. Thus, the correlation was good according to the Jaffe criterion [10].

EXPERIMENTAL

PMR spectra were recorded in $CDCl_3$ on a Bruker WM-250 spectrometer (250 MHz) with TMS internal standard. IR spectra were obtained in KBr disks on a UR-20 spectrometer. The purity of products and R_f values were determined on Silufol UV-254 using solvent systems $CHCl_3$:CH_3OH (19:1, system a; 3:2, system b; 3:1, system c) and C_6H_6:$CHCl_3$ (2:1,

system d). Optical rotation was measured on a SU-3 universal saccharimeter. The preparation of α-chloro-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (**1**) has been reported [11]. Heterocyclic amines were prepared by the literature method [12].

1-Amino-5-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-4,4,8,8-tetramethyl-2,3,6,7-dibenzo-9-oxabicyclo-(3,3,1)-nonane (6). A mixture of α-chloro-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (0.7 g, 0.002 mol) in anhydrous ether (35 mL) and **2** (0.77 g, 0.0025 mol) was treated with freshly prepared Ag_2CO_3 (0.09 g). The reaction was carried out under N_2 with constant stirring for 14 h (20–25°C). The mixture was filtered and evaporated. The resulting syrup was dissolved in $CHCl_3$, treated with activated carbon, and again evaporated in vacuo. Separation over a column (system d, silica gel L 50/100) produced a chromatographically pure product (1.11 g, 70.2 %), R_f 0.72 (system a), mp 115–116°C, $[\alpha]_D^{18}$ +52.6° (*c* 0.5, $CHCl_3$). $C_{34}H_{41}O_{11}N$.

IR spectrum (ν, cm^{-1}): 3479 ($NH_{2\ str}$), 1689 ($NH_{2\ def.}$), 1025-948 (gem-dimethyl), 1720 (C=O), 1120-1040 (C–O–C), 624-586 ($C–H_{ar}$).

PMR spectrum (δ, ppm, J/Hz): 7.0-7.5 (8H, m, aromatic protons), 2.9-3.0 (2H, m, NH_2), 1.45 and 1.47 (12H, s, gem-dimethyl, $4CH_3$), 4.52 (1H, d, $J_{1,2}$ = 8.0, H-1), 5.09 (1H, dd, $J_{2,1}$ = 8.0, $J_{2,3}$ = 10.4, H-2), 3.7 (1H, dd, $J_{3,2}$ = 10.4, $J_{3,4}$ = 3.3, H-3), 5.18 (1H, dd, $J_{4,3}$ = 3.0, $J_{4,5}$ = 9.5, H-4), 3.87 (1H, ddd, $J_{5,4}$ = 9.5, $J_{5,6'}$ = 5.0, $J_{5,6''}$ = 2.5, H-5), 4.11 (1H, H-6′, dd, $J_{6',6''}$ = 12, $J_{6',5}$ = 2.5, C**H**$_2$OCOCH$_3$), 4.22 (1H, H-6″, dd, $J_{6',6''}$ = 12, $J_{6'',5}$ = 5.0, C**H**$_2$OCOCH$_3$), 2.10, 2.03, 1.99, 1.95 (each 3H, m, CO–CH_3).

1-Methylamino-5-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-4,4,8,8-tetramethyl-2,3,6,7-dibenzo-9-oxabicyclo-(3,3,1)-nonane (7) was prepared analogously by condensation of α-chloro-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (0.7 g, 0.002 mol) in anhydrous ether (35 mL) and **3** (0.8 g, 0.0025 mol) in the presence of freshly prepared Ag_2CO_3 (0.09 g). Yield 1.1 g (68.8%), R_f 0.44 (system b), mp 154–155°C, $[\alpha]_D^{17}$ +24.2° (*c* 0.32, $CHCl_3$). $C_{35}H_{43}NO_{11}$.

IR spectrum (ν, cm^{-1}): 2930, 2850, 1470 (CH_3), 3360 (NH), 1380-1370 (gem-dimethyl), 1690-1650 (C=O), 1170, 1130, 1010 (C–O–C), 588 ($C–H_{ar}$).

PMR spectrum (δ, ppm, J/Hz): 7.6-7.0 (8H, m, aromatic protons), 3.25 (1H, s, NH), 1.41, 1.35, 1.32, 1.30 (12H, s, gem-dimethyl), 2.16, 2.08, 1.96, 1.85 (12H, m, $4COCH_3$), 0.78 (3H, m, CH_3), 4.46 (1H, d, $J_{1,2}$ = 8.0, H-1), 5.09 (1H, dd, $J_{2,1}$ = 8.0, $J_{2,3}$ = 9.5, H-2), 3.7 (1H, dd, $J_{3,2}$ = 9.5, $J_{3,4}$ = 3.0, H-3), 5.13 (1H, dd, $J_{4,3}$ = 3.0, $J_{4,5}$ = 9.5, H-4), 3.84 (1H, ddd, $J_{5,4}$ = 9.5, $J_{5,6'}$ = 5.0, $J_{5,6''}$ = 2.5, H-5), 4.10 (1H, H-6′, dd, $J_{6',6''}$ = 12.0, $J_{6',5}$ = 2.5, C**H**$_2$OCOCH$_3$), 4.20 (1H, H-6″, dd, $J_{6',6''}$ = 12, $J_{6'',5}$ = 5.0, C**H**$_2$OCOCH$_3$), 1.96, 1.98, 2.10, 2.03 (each 3H, m, CO–CH_3).

1-*N*-Ethylamino-5-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-4,4,8,8-tetramethyl-2,3,6,7-dibenzo-9-oxabicyclo-(3,3,1)-nonane (8) was prepared analogously by condensation of α-chloro-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (0.7 g, 0.002 mol) in anhydrous ether (35 mL) and **4** (0.84 g, 0.0025 mol) in the presence of freshly prepared Ag_2CO_3 (0.09 g). Yield 1.01 g (63.2%), R_f 0.62 (system b), mp 160–161.5°C, $[\alpha]_D^{17}$ +37.7° (*c* 0.51, $CHCl_3$). $C_{36}H_{45}NO_{11}$.

IR spectrum (ν, cm^{-1}): 2930, 2850, 1470 (CH_3), 3360 (NH), 1728 (C=O), 1262 (C–O–C), 1380 (C–N), 580 ($C–H_{ar}$).

PMR spectrum (δ, ppm, J/Hz): 7.3 (6H, s, aromatic protons), 2.7–3.0 (3H, m, NH–CH_2), 1.36 and 1.33 (12H, s, gem-dimethyl, $4CH_3$), 1.02 (3H, t, $NHCH_3$), 4.46 (1H, d, $J_{1,2}$ = 8.0, H-1), 5.09 (1H, dd, $J_{2,1}$ = 8.0, $J_{2,3}$ = 10.4, H-2), 3.7 (1H, dd, $J_{3,2}$ = 10.4, $J_{3,4}$ = 3.3, H-3), 5.18 (1H, dd, $J_{4,3}$ = 3.0, $J_{4,5}$ = 9.5, H-4), 3.87 (1H, ddd, $J_{5,4}$ = 9.5, $J_{5,6'}$ = 5.0, $J_{5,6''}$ = 2.5, H-5), 4.11 (1H, H-6′, dd, $J_{6',6''}$ = 12, $J_{6',5}$ = 2.5, C**H**$_2$OCOCH$_3$), 4.22 (1H, H-6″, dd, $J_{6',6''}$ = 12, $J_{6'',5}$ = 5.0, C**H**$_2$OCOCH$_3$), 1.93, 1.98, 2.10, 2.21 (each 3H, m, CO–CH_3).

1-[2-(3-Indolylethylamino)]-5-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-4,4,8,8-tetramethyl-2,3,6,7-dibenzo-9-oxabicyclo-(3,3,1)-nonane (9) was prepared analogously by condensation of α-chloro-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (0.7 g, 0.002 mol) in anhydrous ether (35 mL) and **5** (1.13 g, 0.0025 mol) in the presence of freshly prepared Ag_2CO_3 (0.09 g). Yield 1.05 g (55.7%), R_f 0.58 (system c), mp 163–164°C, $[\alpha]_D^{18}$ +31.3° (*c* 0.6, $CHCl_3$). $C_{44}H_{50}N_2O_{11}$.

IR spectrum (ν, cm^{-1}): 3315 (indole NH), 2920 (NH), 1320-948 (gem-dimethyl), 1726 (C=O), 1220, 1010 (C–O–C), 580 ($C–H_{ar}$).

PMR spectrum (δ, ppm, J/Hz): 10.7 (1H, s, tryptamine NH), 7.5–6.8 (12H, m, aromatic protons), 3.0–2.5 (4H, m, C**H**$_2$–C**H**$_2$–NH), 1.32 and 1.41 (12H, s, gem-dimethyl, $4CH_3$), 4.43 (1H, d, $J_{1,2}$ = 8.0, H-1), 5.05 (1H, dd, $J_{2,1}$ = 8.0, $J_{2,3}$ = 9.5, H-2), 3.75 (1H, dd, $J_{3,2}$ = 9.5, $J_{3,4}$ = 3.0, H-3), 5.20 (1H, dd, $J_{4,3}$ = 3.0, $J_{4,5}$ = 9.5, H-4), 3.84 (1H, ddd, $J_{5,4}$ = 9.5, $J_{5,6'}$ = 5.0, $J_{5,6''}$ = 2.5, H-5), 4.11 (1H, H-6′, dd, $J_{6',6''}$ = 12, $J_{6',5}$ = 2.5, C**H**$_2$OCOCH$_3$), 4.22 (1H, H-6″, dd, $J_{6',6''}$ = 12, $J_{6'',5}$ = 5.0, C**H**$_2$OCOCH$_3$), 1.93, 1.98, 2.10, 2.21 (each 3H, m, CO–CH_3).

REFERENCES

1. V. G. Granik and N. B. Grigor′ev, *Nitrogen Oxide, a New Direction in Drug Discovery* [in Russian], Vuzovskaya Kniga, Moscow, 2004, pp. 108-115.
2. R. M. Lagidze, N. K. Iremadze, and I. G. Abesadze, *Soobshch. Akad. Nauk Gruz. SSR*, **127**, 1, 85 (1987).
3. N. Sidamonidze, R. Vardiashvili, M. Isakadze, and L. Djaniashvili, *Pharm. Chem. J.*, **41**, 3, 131 (2007).
4. A. F. Bochkov, V. A. Afanas′ev, and G. E. Zaikov, *Formation and Cleavage of Glycoside Bonds* [in Russian], Nauka, Moscow, 1978.
5. M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc.*, **107**, 3902 (1985).
6. P. H. Rouvray, *Chemical Application of Topology and Graph Theory*, Elsevier Science Publ., Amsterdam, 1983.
7. G. Gamziani and M. Gverdtsiteli, *Isomery Phenomenon from Point of View of Mathematical Chemistry*, Metsniereba, Tbilisi, 1992.
8. M. Gverdtsiteli, G. Gamziani, and I. Gverdtsiteli, *The Contiguity Matrices of Molecular Graphs and Their Modifications*, Tbilisi Univ. Press, Tbilisi, 1996.
9. K. Kupatadze, T. Lobzhanidze, and M. Gverdtsiteli, *Algebraic Chemical Investigation of Some Organic Molecules and Their Transformations*, Publ. Univ., Tbilisi, 2007.
10. Yu. A. Zhdanov and V. I. Minkin, *Correlation Analysis in Organic Chemistry* [in Russian], Rost. Univ., Rostov, 1966.
11. K. Freudenberg and K. Soff, *Ber.*, **69**, 1245 (1936).
12. A. Kiriyakid, M. Lursmanashvili, and I. Abesadze, *Izv. Akad. Nauk Gruz.*, **3**, 3 (2003).