NEW N-GLUCOSYLATED SUBSTITUTED ANILINES

Vsevolod Pogrebnoi

Institute of Chemistry of the Academy of Sciences of Moldova, 3, Academiei str., Chisinau MD-2028, Moldova

e-mail: seva.antivirus@gmail.com; phone: (+373 22) 739 754; fax: (+373 22) 739 954

Abstract. The reaction of (+)-D-glucose 1 with 4-chloroaniline 6b or 3,5-dibromoaniline 12 leads almost exclusively to the β-configuration of N-glucosylated anilines 7b and 13. Acetylated derivatives 8b, 14 and 15 were obtained by dissolving/suspending substances 7b and 13 in Ac2O/Py mixture. The acetylation of 2-(3,5-dibromophenylamino)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol 13 is less selective than in the case of the 2-(4-chlorophenylamino)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol 7b and leads to compounds 2-(acetoxymethyl)-6-(3,5-dibromophenylamino)tetrahydro-2H-pyran-3,4,5-triyi triacetate 14 and 2-(acetoxymethyl)-6-(3,5-dibromophenylamino)-5-hydroxytetrahydro-2H-pyran-3,4-diyl diacetate 15 in a 2:1 ratio. The product 14 is formed with greater selectivity and in a higher yield (up to 80%) when the reaction is catalyzed by DMAP and stored for one week at +4°C.

Keywords: N-glucosylated anilines, (+)-D-glucose, 4-chloroaniline, 3,5-dibromoaniline, Convolutamydines A-E.

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Introduction

N-Glycosylated anilines represent an important product scaffold cluster by virtue of their bioactivity and as intermediates for generating further molecular complexity including natural compounds [1], for example some natural alkaloids. The vital roles played by sugars in biological systems continue to be unravelled. It is known that, various drugs, amino acids, sugars and many other chiral natural compounds show different influence on human organism, their biological properties being directly dependent on chirality. That is why the “structure-property” relationship should be studied very well. From the other side, properties are determined by the structure. It means, construction of chemically pure and defined molecule is an interesting and important goal in synthetic chemistry.

Langer et al. [1,2] has shortly offered the opinion that the preparation of analogues of N-glycosylated indolinones in high yields remains an important problem of carbohydrate and medicinal chemistry. This challenge also applies to the related problem of synthesis of N-linked alkaloids. For example, Kamano, Y. et al. [3], reported the isolation of the alkaloids - Convolutamydines A, B, and C from bryozoan Amathia convoluta, see Figure 1. In contrast to the pharmacologically inactive non-glycosylated indigo, N-glycosylated indigo demonstrate a considerable growth inhibitory activity toward various human tumor cell lines [4,5].

Our approaches to N-glucosylated indoline-2,3-dione 4 from (+)-D-glucose 1 and N-glucosylated 3-hydroxy-2-oxindole 5 are presented below. They show benefit from the rapid advances in mainstream carbohydrate chemistry, allowing for convenient integration in glucosylated Convolutamydine A-E and analogues of structure 5 preparation (see Figure 1).

![Figure 1. Synthesis of N-glucosylated indoline-2,3-dione (4).](image-url)
The main purpose of the present research was to test the effectiveness of this approach for the synthesis of halogen phenylamino-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol triacetates from the corresponding intermediates 3 (see Figure 1). It has already been demonstrated that such type compounds are suitable building units for the synthesis of a variety of non-halogenated isatin-N-glycosides [1,2]. We also report in this paper the preparation of 3,5-dibromoaniline 12.

Results and discussion

It was reported [1], that similar aniline-\(N\)-glucosides 7a were prepared from corresponding anilines (R=H, Me, i-Pr, t-Bu) and \((+)-D\)-glucose 1. The formed product 7a was directly used for the next step (see Scheme 1). However, some of the derivatives of glycosides can be isolated as pure \(\beta\)-anomers 8a, whereas the others contain a small amount of the corresponding \(\alpha\)-anomer [1,2].

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\begin{align*}
\text{Scheme 1. Syntheses of } N\text{-glucosylated 4-substituted anilines 8a and 8b [1].}
\end{align*}
\]

In the course of our studies the (2R,3R,4S,5S,6R)-2-(4-chlorophenylamino)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol 7b was prepared according to the reported method [1] primarily by reason of convenience: medium solubility of \((+)-D\)-glucose 1 in MeOH and easy removal from the excess of aniline by filtration and washing with cool MeOH, provides ready access to the solid aminoglycoside, which is slightly soluble in MeOH. A mixture of \((+)-D\)-glucose 1 and 4-chloroaniline 6b was refluxed for 12 hours (see Scheme 1). TLC of the reaction mixture indicated the disappearance of the starting glucose 1 and an increase in the intensity of the neighbouring spot. On keeping the solution overnight in the refrigerator an adduct precipitated that was easily isolated by filtration, being then identified as compound 7b. It had m.p. 154-156 °C and characteristic IR absorption bands \(\nu_{OH}\) at 3271 and 3209 cm\(^{-1}\), the primary (C-6) and secondary (C-2, C-3 and C-4) nature of the alcohol functions being confirmed by the \(^1\)H NMR spectrum (triplet at \(\delta_H 4.44-4.47\) ppm with a splitting constant \(J=5.8\) Hz and three doublets at \(\delta_H 4.88-4.90, 4.92-4.9\) and 5.00-5.02 ppm with splitting constants \(J=5.4, J=5.2\) and \(J=4.7\) Hz. NH group shows doublet at \(\delta_H 6.46-6.48\) ppm. Moreover, \(^1\)H NMR spectrum has resonances at \(\delta_H 6.67-6.69\) ppm (C-2'-H and C-6'-H, doublet, \(J=8.8\) Hz) and \(\delta_H 7.10-7.12\) ppm (C-3'-H and C-5'-H, doublet, \(J=8.8\) Hz), indicating that compound 7b is an aniline. Additionally, absorption in the low-field region of its \(^{13}\)C NMR spectrum confirmed the presence of aromatic carbons at \(\delta_C 115.06\) ppm (C-2' and C-6'), 120.7 ppm (C-4'), 128.92 ppm (C-3' and C-5') ppm and 146.7 ppm (C-1').

In fact compound 7b shows in the \(^1\)H NMR spectrum a clear triplet at \(\delta_H 4.30-4.34\) ppm with the magnitude of a spin-spin coupling constant \(J=8\) Hz and an important peak at 883.8 cm\(^{-1}\) in its IR-spectrum, which is characteristic for a \(\beta\)-anomer.

The reaction of compound 7b with \((+)-D\)-glucose 1 was slow and only after 48 hrs provided a solid compound with m.p. 146-149°C. The substance 8b was obtained in 97% yield, being identified as (2R,3R,4S,5S,6R)-2-(4-chlorophenylamino)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol 8b on the basis of its NMR spectroscopic data. Thus, the \(^1\)H NMR spectrum of it showed in the low-field region two singlets and a doublet at \(\delta_H 1.95, 1.97, 2.00\) ppm characterizing four acetate groups, according to the integral. The \(^1\)H NMR spectrum of compound 8b also contains two doublets of aromatic protons, centered at \(\delta_H 6.75\) ppm (2H, C-2'-H and C-6'-H, \(J=8.9\) Hz) and \(\delta_H 7.14\) ppm (2H, C-3'-H and C-5'-H, \(J=8.8\)Hz) and a doublet of NH group at \(\delta_H 6.71\) ppm with the spin-spin coupling constant \(J=9.8\) Hz. The \(^{13}\)C NMR spectroscopic data totally confirm the structure 8b, see experimental part. Thus, the preparation of (2R,3R,4S,5S,6R)-2-(4-chlorophenylamino)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol 8b \(via\) aniline-N-glucoside 7b has been successfully reproduced by us.

It was found that the 4,6-dibromohydroxyxindole nucleus exhibit a potent activity in the differentiation of HL-60 human promyelocytic cells [3,6]. Therefore, as a part of the program aimed at developing new N-glycosylated oxindoles, we supposed, that the 3,5-dibromoaniline 12 scaffold has potential to enhance the selectivity. As obvious precursor for the synthesis of glucosylated Convolutamydines A-E 5, 3,5-dibromoaniline 12 was prepared by initial bromination of 4-nitroaniline 9, followed by deamination of aniline 10, to form 3,5-dibromonitrobenzene 11.
As it can be seen from Scheme 2, the reaction of 12 with (+)-D-glucose 1 was slow and only after 24 hrs provided a solid compound with m.p. 169-170°C. The substance obtained in 97% yield was identified as (2R,3R,4S,5S,6R)-2-(3,5-dibromophenylamino)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol 13 on the basis of its 1H NMR spectrum, which showed in the low-field region signals at δ 6.86 ppm and δ 6.95 ppm (aromatic), δ 6.89 ppm (NH), δ 4.52 ppm, δ 4.96 ppm, δ 4.97 ppm and δ 5.05 ppm (C-6-OH, C-4-OH, C-2-OH and C-3-OH, respectively). Moreover, in its 1H spectrum the multiplets at δ 3.10-3.24 ppm (C-2-H, C-3-H, C-4-H, C-5-H, C-6-H) and triplet centred at δ 4.36 ppm (C-1-H) are present. The IR-spectrum showed a low intensity band at 892.4 cm-1 assigned to the C-1-H scissoring of the protons in the β-anomer. Similarly, the 1H NMR spectrum indicated the presence of C-1-H (a triplet at δ 4.36 ppm with a splitting constant J = 8 Hz). However, 1H NMR spectrum shows two additional signals: a doublet attributable to three protons for methanol at δ 3.17 ppm and a quartet of one proton at δ 6.95 ppm (OH), shielded by an additional carbon, which appears in 13C NMR spectrum at δ 49.10 ppm. Finally, the structure of the product is considered to be 13 on the basis of its elemental analysis, as well. The formation of intermolecular complex 13 has been rationalized by considering the participation of the hydroxyl, as well as NH groups in the addition of 12 with (+)-D-glucose in MeOH medium.

The acetylation reaction of 13 was performed with acetic anhydride in pyridine and lead to esters 14. The reaction was very slow (one week) and after work-up two main products in the obtained mixture were then separated by column chromatography over silica gel.

As a result, pure 14 was isolated as the least polar product with m.p. 72-73°C in 35% yield and its structure has been proved by NMR. The 1H NMR spectrum of it contains singlets at δ 2.03 ppm, δ 2.06 ppm, δ 2.07 ppm, δ 2.11 ppm (AcO groups), a doublet centered at δ 4.86 ppm (J = 9.7 Hz) (NH group), multiplets at δ 3.86, 4.68, 5.00, 5.04, 5.37 ppm (C2-H, C3-H, C4-H, C5-H, C6-H, correspondingly), multiplets at δ 4.14 and 4.23 ppm (CH3), and doublet of aromatic protons at δ 6.74 ppm (2H, J = 1.5, C-2′′-H, C-6′′-H) and δ 7.11 ppm (1H, t, J = 1.5, C-4′′′-H).

Moreover, its formulation as an ester has been sustained by peaks in higher field 13C NMR spectrum at δ 27.2 ppm (C-5), 68.9 (C-4), 72.5 (C-3), 71.0 (C-2), 83.6 (C-1) and 146.7 ppm (C-1′) and peaks in lower field at δ 62.3 (C-6), 115.9 (C-2′, C-6′), 123.2 (C-3′, C-5′) and 125.1 ppm (C-4′). This resonance pattern differs markedly from that observed for the initial compound 13. The comparative examination also suggests that four acetyl group functions should have eight peaks as well. This is consistent with the observation of signals at δ 20.6 (CH3), 20.65 (CH3), 20.7 (CH3), 20.8 (CH3), 170.7 (C=O), 169.6 (C=O), 169.9 (C=O) and 171.3 (C=O). The IR-spectrum showed bands at 1740 cm-1, 1588 cm-1, 3371 cm-1, 915 cm-1 and 671 cm-1 assigned to the COO, aromatic, NH, β-glucopyranoside and C-Br, respectively.

Additionally, another product was isolated, which presumably corresponded to the structure 15. According to NMR data, the isolated product is a mixture of compounds 14 and 15 in 2:1 ratio, which has been determined by integration of the signals belonging to the acetate groups. It could be easily identified according to 13C NMR spectrum by the double set of signals: four C=O groups at δ 169.6, 169.9, 170.7 and 171.3 ppm for compound 14, and three C=O groups for compound 15 at δ 169.1, 169.5 and 170.4 respectively. Similarly, double set of signals has been noted for pyranic (δ 60-83 ppm) and aromatic (δ 115-147 ppm) parts of molecules of the discussed derivative (see experimental
part). Thus, the $^1$H NMR spectrum shows multiplets at $\delta_H$ 3.85-3.90, 4.01-4.30, 4.99-5.07, 5.16-5.20 and 5.30-5.46 ppm, which are characteristic for pyramic part (CH and OH), two doublets at $\delta_H$ 6.74 and 7.00 ppm and two triplets centered at $\delta_H$ 7.10 and 7.14 ppm (aromatic), four singlets at $\delta_H$ 2.04, 2.05, 2.06 and 2.07 ppm for compound 14, a singlet at $\delta_H$ 2.03 ppm and a doublet centered at $\delta_H$ 2.08 ppm for compound 15, respectively.

Catalysis by pyridine is of the nucleophilic type and it is known that 4-(N,N-dimethylamino)pyridine is a better catalyst when pyridine fails. Indeed, compound 13 readily undergoes reaction with acetic anhydride under analogous conditions in presence 4-(N,N-dimethylamino)pyridine to yield up to 90% compound 14.

Conclusions

The present work demonstrates that interaction of 4-chloro- and 3,5-dibromo- substituted anilines with (+)-D-glucose affords N-glycosylated adducts 7b and 13 as $\beta$-anomers. The position and steric course of further esterification are catalytically dependent. We confirmed that in the case of 4-chloro substituted aniline reaction with Ac_2O in Py occurs mainly to give tetra-acetate 8b. On the contrary, reaction of 3,5-dibromo substituted aniline gives a mixture of adducts 14 and 15 in a 2:1 ratio with overall yield 65%. In the case when the reaction was catalysed by 4-(N,N-dimethylamino)pyridine only compound 14 was obtained in 80% overall yield. The structures of all new compounds 13, 14 and 15, including configurations of anomeric carbon atoms, were characterized through IR and NMR spectroscopic methods.

Experimental

All used solvents were of reagent quality, and all commercial reagents were used without additional purification. M. p.s (uncorrected) were determined on a Boetius apparatus. IR spectra were recorded on a Spectrum 100 FT-IR spectrophotometer (Perkin - Elmer) using the universal ATR sampling accessory. $^1$H and $^13$C NMR spectra were registered in CDCl$_3$ and DMSO-d$_6$ 2-2% solution on a “Bruker-Avance III” (400.13 and 100.61 MHz) spectrometer.

General procedure for the synthesis of N-glucosylated anilines 7b and 13.

To a solution of (+)-D-glucose 1 (2g, 0.011 mol) in 25 mL of absolute methanol corresponding aniline (6b or 12) (0.013 mol) was added. The mixture was refluxed for 24 hours. After completion of the reaction (TLC control, solvent system 2% MeOH in CH$_2$Cl$_2$) the mixture was stored in refrigerator at sub-zero temperature so long, as white volume is being precipitated. The precipitate was filtered and washed with methanol and dried at room temperature.

(2R,3R,4R,5R,6R)-2-(4-chlorophenylamino)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol 7b. White solid. Yield 95 %. M. p. 154-156°C (MeOH). [α]$_{D}^{20}$.41.0 (c 0.068, DMSO). IR-spectra (ν/cm$^{-1}$): 3271.5, 3209.1 (OH), 1523.4 (NH), 883.8 (C-1-H), 683.3 (C-C). $^1$H NMR (400 MHz, DMSO- $d_6$, δ, ppm, /Hz): 3.07-3.27 (4H, m, C-2-H, C-3-H, C-4-H, C-5-H), 3.39-3.45 (1H, m, C-6-H), 3.61-3.66 (1H, m, C-6-H), 4.30-4.34 (1H, t, C-1-H, J=8), 4.44-4.47 (1H, t, C-6-OH, J=5.8), 4.88-4.90 (1H, d, C-4-OH, J=5.4), 4.92-4.93 (1H, d, C-2-OH, J=5.2), 5.00-5.02 (1H, d, C-3-OH, J=4.7), 6.46-6.48 (1H, d, NH, J=7.5), 6.67-6.69 (2H, d, C-2'-H, C-6'-H, J=8.8), 7.10-7.12 (2H, d, C-3'-H, C-5'-H, J=8.8). $^13$C NMR (100.6 MHz, DMSO-$d_6$): 61.3 (C-6), 70.6 (C-3), 73.5 (C-2), 77.8 (C-3), 78.1 (C-5), 85.3 (C-1), 115.0 (C-2'), 120.7 (C-4'), 128.9 (C-3', C-5'), 146.8 (C-1'). Calculated, %: C 49.75; H 5.57; N 4.83. C$_{12}$H$_{15}$Br$_2$NO$_5$. Found, %: C 49.80; H 5.60; N 3.40.

(2R,3R,4S,5S,6R)-2-(3,5-dibromophenylamino)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol 13. White solid. Yield 97 %. M. p. 169-170°C (MeOH). [α]$_{D}^{20}$.62.40 (c 0.05, DMSO). IR-spectra (ν/cm$^{-1}$): 3367.5, 3210.1, 3073.2 (OH); 1518.0 (NH), 892.4 (C-1-H), 668.2 (C-Br), 1574.5 (aromatics), 3367-3073 (OH). $^1$H NMR (400 MHz, DMSO-$d_6$, δ, ppm, /Hz): 3.39-3.65 (1H, ddd, J=11.8, 5.8, 1.9, C-6-H), 3.1 (2H, m, C-4-H, C-2-H), 3.24 (2H, m, C-5-H, C-3-H), 3.17 (3H, d, J=5.2, CH$_3$OH), 4.18 (1H, q, J=5.2, CH$_2$OH), 4.36 (1H, t, J=8, C-1-H), 4.52 (1H, t, J=5.8, C-6-OH), 4.96, (1H, d, J=1.7, C-4-OH), 4.97 (1H, d, J=1.4, C-2-OH), 5.05 (1H, d, J=4.8, C-3-OH), 6.89 (1H, d, J=7.8, NH), 6.86 (2H, d, J=7.6, C-2'-H, C-6'-H), 6.95 (1H, t, J=1.6, C-4'-H). $^13$C NMR (100.6 MHz, DMSO-$d_6$): 49.1 (MeOH), 61.3 (C-6), 70.7 (C-4), 73.5 (C-2), 77.8 (C-3), 84.5 (C-1), 115.1 (C-2' and C-6'), 121.5 (C-4'), 123.1 (C-3' and C-5'), 150.7 (C-1'). Calculated, %: C 34.89; H 3.66; N 3.39. C$_{12}$H$_{15}$Br$_2$NO$_5$. Found, %: C 34.94; H 3.64; N 3.41.

Procedure for the synthesis of compound 8b.

The anilide 7b is maximally dissolved in dry pyridine under stirring (for every hydroxyl group 1.8-2.0 eq. of pyridine are used) and cooled in an ice bath to 0°C. Then, freshly distilled acetic anhydride is rapidly added (for every hydroxyl group 1.5-1.6 eq. of acetic anhydride are used). Stirring is continued at the same temperature until a homogeneous solution appeared (about 3 hours). The mixture was hold for 24-48 hours in a refrigerator without stirring. After completion of the
reaction (TLC control, system hexane-ethyl acetate 4:1), the mixture was poured into ice-water (1:2) and extracted with ethyl acetate (4x30 mL). The combined organic phases were washed with sodium hydrogen carbonate solution, water and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting white solid mass was recrystallised from methanol. The bittter was evaporated and recrystallised again. The obtained product is white solid.

### General procedure for the synthesis of compounds 14 and 15.

**Method A:** The anilide 13 is maximally dissolved in dry pyridine under stirring (for every hydroxyl group 1.8-2.0 eq. of pyridine are used) and cooled in an ice bath to 0°C. Then, freshly distillated acetic anhydride is rapidly added (for every hydroxyl group 1.5-1.6 eq. of acetic anhydride are used). Stirring is continued at the same temperature until a homogeneous solution appeared (about 3 hours). The mixture was hold for 24-48 hours in a refrigerator without stirring. After completion of the reaction (TLC control, system hexane-ethyl acetate 4:1), the mixture was poured into ice-water (1:2) and extracted with ethyl acetate (4x30 mL). The combined organic phases were washed with sodium hydrogen carbonate solution, water and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting oily mass was purified by column chromatography on silica gel, using as eluent hexane-ethyl acetate (6:1 to 3:1).

**Method B:** The anilide 13 is maximally dissolved in dry pyridine under stirring. For every hydroxyl group is used 1.8-2.0 eq. of pyridine, and cooled in an ice bath to 0°C. Then, freshly distilled acetic anhydride is added rapidly. For every hydroxyl group is used 1.5-1.6 eq. of acetic anhydride. Then 10 mol% of DMAP (catalyst) was added and stirring was continued at the same temperature until a homogeneous solution appeared (about 3 hours). The mixture was hold for one week in a refrigerator without stirring. After completion of the reaction (TLC control, system hexane-ethyl acetate 4:1), the mixture was poured into ice-water (1:2) and extracted with ethyl acetate (4x30 mL). The combined organic phases were washed with sodium hydrogen carbonate solution, water and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting oily mass was purified by column chromatography on silica gel, using as eluent hexane-ethyl acetate (6:1 to 3:1).

### (2R,3R,4S,5R,6R)-2-(Acetoxymethyl)-6-(4-chlorophenylamino)tetrohydro-2H-pyran-3,4,5-triyl triacetate 8b

White solid. Yield 97 %. M. p. 146-149°C (MeOH). [α]_D^20 = -48.6 (c 0.076, CHCl3). IR-spectra (ν/cm⁻¹): 1059.5, 1180.7 (C-O-C), 1511.7 (NH), 878.9 (C=H), 688.4 (C=Cl). 1H NMR (400 MHz, DMSO-d₆, δ, ppm, J/Hz): 1.95 (3H, s, CH₃CO), 2.00 (3H, s, CH₃CO), 2.08 (3H, s, CH₃CO), 3.86 (1H, ddd, J=10.1, 6.3, 2.1, C6-H), 4.14 (1H, dd, J=12.1, 2.1, C-6-H), 4.23 (1H, dd, J=12.1, 6.3, C-6-H), 4.68 (1H, t, J=8.8, C-1-H), 5.00 (1H, t, J=9.5, C-1-H, J=9.1, C-2-H), 5.04 (1H, t, J=9.7, C-4-H), 5.04 (1H, d, J=8.8, NH), 5.37 (1H, τ, J=9.1, C-3-H), 6.74 (2H, d, J=1.5, C-2'-H, C-6'-H), 7.11 (1H, t, J=1.5, C-4'-H). 13C NMR (100.6 MHz, CDCl₃): 20.6-20.8 (MeOH). 20.7-20.8 (MeOH). 68.7-68.5, 68.9, 70.2, 71.1, 72.6, 72.6, 79.7, 83.5, (C1-C6), 115.9, 116.1 (C-2', C-6'), 123.4, 123.4 (C-4'), 125.1, 125.4 (C-3', C-5'), 146.7 1472 (C-1'), 169.1, 169.5, 169.6, 169.9, 170.4, 170.7, 171.3 (C=O).
2.6-Dibromo-4-nitroaniline 10
To a heated solution (up to 65°C) of 4-nitroaniline 9 (11 g, 0.08 mol) in 100 mL of glacial acetic acid under stirring is added drop wise a solution of bromine (26 g, 0.16 mol) in 60 mL of glacial acetic acid for 2 hours. After dropping of all bromine, the mixture was stirred for another 1.5 hours at the same temperature. The mixture was allowed to cool up to room temperature, next it was poured into a mixture, consisting of 500 mL of water and 250 g of ice and hold for 1.5 hours. The precipitate was filtered and washed 3 times with water to remove residual of acetic acid and dried at 100°C, getting 22 g of product (melting at 199-200°C). Yield 95%. Further recrystallization from ethylene glycol monomethyl gives yellow-green crystals (prisms). Yellow-green prisms. M. p. 201-202°C. IR-spectra (ν/cm⁻¹): 3417, 1564 (NH), 1525, 1389 (NO₂), 695 (C-Br). ¹H NMR (400 MHz, DMSO-d₆, δ, ppm, J/Hz): 7.30 (2H, s, NH), 8.22 (2H, s, C-3-H and C-5-H). ¹³C NMR (100.6 MHz, CDCl₃): 105.77 (C-Br), 128.3 (C-3 and C-5), 136.9 (C-4), 149.5 (C-1). Calculated, %: C 24.35; H 1.36; N 9.47. C₆H₄Br₂N₂O₂. Found, %: C 24.42; H 1.34; N 9.51.

3,5-Dibromonitrobenzene 11
To a heated up to 70°C solution of 2,6-dibromo-4-nitroaniline 10 (20 g, 0.067 mol) in 160 mL of ethanol, concentrated sulfuric acid (11 mL) is slowly added under stirring until the mixture become a homogeneous system. Next, sodium nitrite (10 g, 0.14 mol) is added under stirring. Stirring was continued for 2 hours in strongly alkaline medium (pH 11-12). To a heated solution (up to 70°C) of 4-nitroaniline 9 (11 g, 0.08 mol) in 100 mL of glacial acetic acid under stirring is added drop wise a solution of bromine (26 g, 0.16 mol) in 60 mL of glacial acetic acid for 2 hours. After dropping of all bromine, the mixture was stirred for another 1.5 hours at the same temperature. The mixture was allowed to cool up to room temperature, next it was poured into a mixture, consisting of 500 mL of water and 250 g of ice and hold for 1.5 hours. The precipitate was filtered and washed 3 times with water to remove residual sodium nitrite. Further recrystallization from ethanol gives 14 g of product 11. The product is an orange solid. Yield 80%. M. p. 110°C (EtOH). IR-spectra (ν/cm⁻¹): 1528, 1336 (NO₂), 650 (C-Br). ¹H NMR (400 MHz, CDCl₃, δ, ppm, J/Hz): 7.98-7.99 (1H, t, J=1.6), 8.31 (2H, d, J=1.6). ¹³C NMR (100.6 MHz, CDCl₃): 123.47 (C-3 and C-5), 116.51 (aromatics), 670 (C-Br). ¹C NMR (100.6 MHz, CDCl₃): 105.77 (C-Br), 128.3 (C-3 and C-5), 136.9 (C-4), 149.5 (C-1). Calculated, %: C 25.65; H 1.08; N 4.99. C₆H₃Br₂NO₂. Found, %: C 25.72; H 1.06; N 5.02.

3,5-Dibromoaniline 12
To a solution of 3,5-dibromonitrobenzene 11 (10g, 0.035 mol) in a 1:1 mixture of ethanol and THF (200 mL) tin(II) chloride dihydrate (40g, 0.175 mol) was added portionwise under stirring. After reaction solvents were removed in vacuo, 250 mL of water was added into remained orange liquid and dry alkali is added under stirring. Stirring was continued for 2 hours in strongly alkaline medium (pH 11-12). Next, the mixture was poured into separatory funnel, extra 150 mL of water was added. The reaction was extracted with diethyl ether (4x40 mL), the combined organic phases were washed with water to remove residual of alkali, dried over anhydrous sodium sulfate and the solvent was removed. The resulting brown mass was purified by column chromatography on silica gel, using as eluent system petroleum ether-ethyl acetate (12:1). As a result, 7.5 g of product 12 have been obtained. Light brown solid. Yield 80%. M. p. 110°C (EtOH).

References