# HEXYLAMINIUM BROMIDES DERIVATIVES OF D-GLUCOPYRANOSE

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**Quaternary aminium salts (QAS) are extensively used in various applications. They are present in fabric softeners and corrosion inhibitors, they act as fungicides, pesticides and insecticides, they reveal antibacterial and antifungal activities employed in antimicrobial drugs, and they are ingredients of shampoos and hair conditioners. Therefore, global use of QAS in industry, agriculture, healthcare and domestic approaches is doubtless. Although toxicity of some QAS has been reported, majority of these compounds were reported as non-toxic or of low toxicity. Therefore, QAS are generally believed to be safe [1,2].**

A new series of quaternary aminium bromides have been synthesized in reaction of 6-bromohexyl 2',3',4',6'-tetra-*O*-acetyl-α-D-glucopyranoside (**αBr6GAc**) and 6-bromohexyl 2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranoside (**βBr6GAc**) with two tertiary amines: pyridine and trimethylamine according to the Menschutkin's procedure (Menschutkin 1890) gave quaternary aminium salts.

Per-*O*-acetylated sugar was treated with 6-bromohexanol in presence of $BF_3 \cdot Et_2O$ as a catalyst (Helferich method). Products of this reaction were: α- and β- 6-bromohexyl 2',3',4',6'-tetra-*O*-acetyl-D-glucopyranosides. For the reaction time 4 h the 1,2-*trans* glycoside (β anomer) was isolated as a major product, extending reaction time to 72 h allowed to synthesize and isolate 1,2-*cis* glycoside (α anomer). Products were isolated and purified by column chromatography using silica gel as stationary phase and acetone : hexane (1:6; v:v) as mobile phase (Scheme 1).

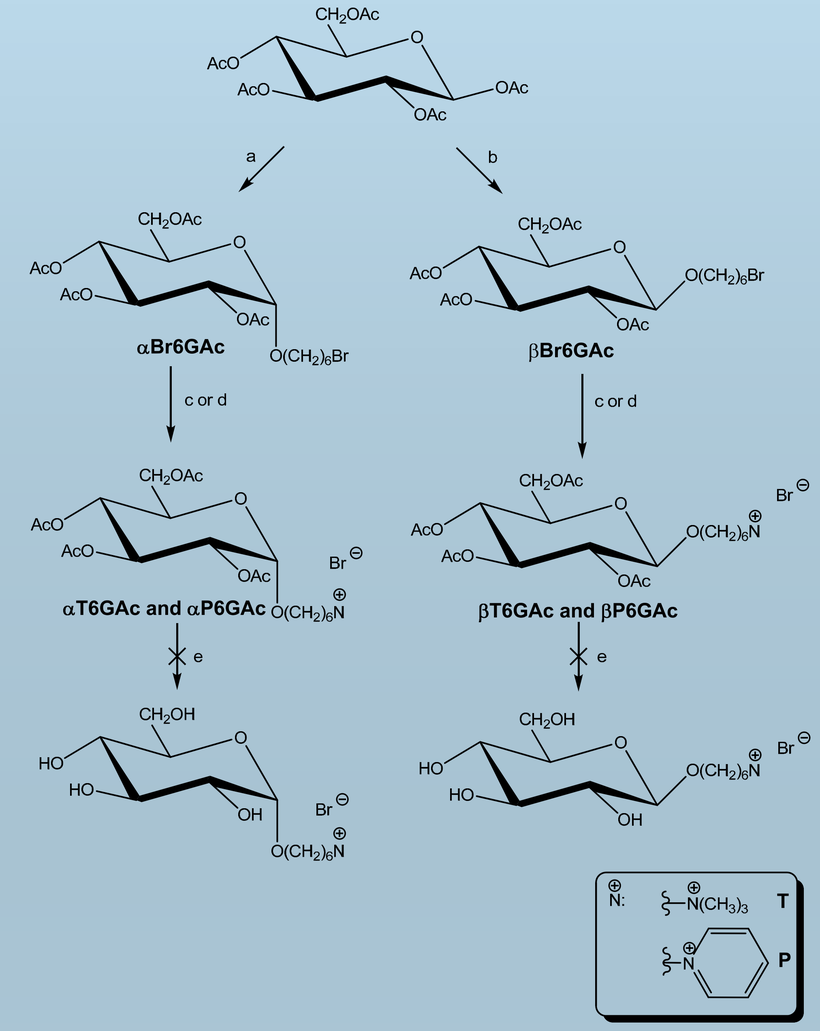
Next both 6-bromohexyl 2',3',4',6'-tetra-*O*-acetyl-α-D-glucopyranoside (**αBr6GAc)** and 6-bromohexyl 2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranoside (**βBr6GAc**) were placed in screwed ampoules and heated at 70 °C with pyridine or ethanolic solution of trimethylamine. Reactions were carried out until substrate was gone (observed by TLC) (Scheme 1). Products were isolated in very good yields, 90-99% and analysed by NMR spectra (Table 1).

Last step was to de-*O*-acetylate previously synthesized aminium bromides: **βT6GAc**, **βP6GAc**, **αT6GAc** and **αP6GAc**. QAS's were dissolved in methanol and treated with 0.82 M MeONa/MeOH. Reaction was carried out in room temperature for 24h. Next $H^+$ ion-exchanging resin was added to neutralize solution. After removal of resin the product was concentrated. After spectral analysis the products were not identified. Problem with achieving desired de-*O*-acetylated products can be explained by interaction of QAS's and resin. Due to their ionic character resin strongly binds product and do not allow to be separated (Scheme 1).

Due to problems with de-*O*-acetylation procedure different approach was taken under consideration, **αBr6GAc** and **βBr6GAc** were de-*O*-acetylated with procedure described previously. The products: 6-bromohexyl α-D-glucopyranoside (**αBr6G**) and 6-bromohexyl β-D-glucopyranoside (**βBr6G**) were isolated and treated with pyridine and trimethylamine in EtOH (procedure described above). The corresponding aminium bromides: **βT6G**, **βP6G**, **αT6G** and **αP6G** were isolated with very good yields (90-98%) and fully characterizes by NMR (Table 1) and MALDI-TOF MS spectra.

The structures of isolates were determined by spectral analysis including: $^1$H NMR, $^{13}$C NMR, COSY and HSQC (Table 1) and MALDI-TOF MS.

All quaternary aminium bromides were tested for mutagenic activity using Ames test on *Salmonella typhimurium* TA98 strain. Compounds were tested in concentrations ranging from 4 μg/plate to 2 mg/plate, results were compared to negative (**C,** water) and positive control (**IQ,** 2-amino-3-methylimidazo[4,5-f]chinoline, 10 μg/plate). Any of synthesized QAS's did not reveal considerable mutagenic properties (Fig. 1).




**Scheme 1:** Reagents and conditions; **a**: $HO(CH_2)_6Br$, $BF_3 \cdot Et_2O/CH_2Cl_2$, 1h 0°C -> 72h, RT ; **b**: $HO(CH_2)_6Br$, $BF_3 \cdot Et_2O/CH_2Cl_2$, 1h, 0°C -> 4h, RT; **c**: $N(CH_3)_3$/EtOH, 70°C, 5h; **d**: Py, 70°C, 24h; **e**: 0.82 M MeONa/MeOH, RT, 24h

**Figure 1.** Ames test results for QAS's, **C** –negative control **IQ** - positive control

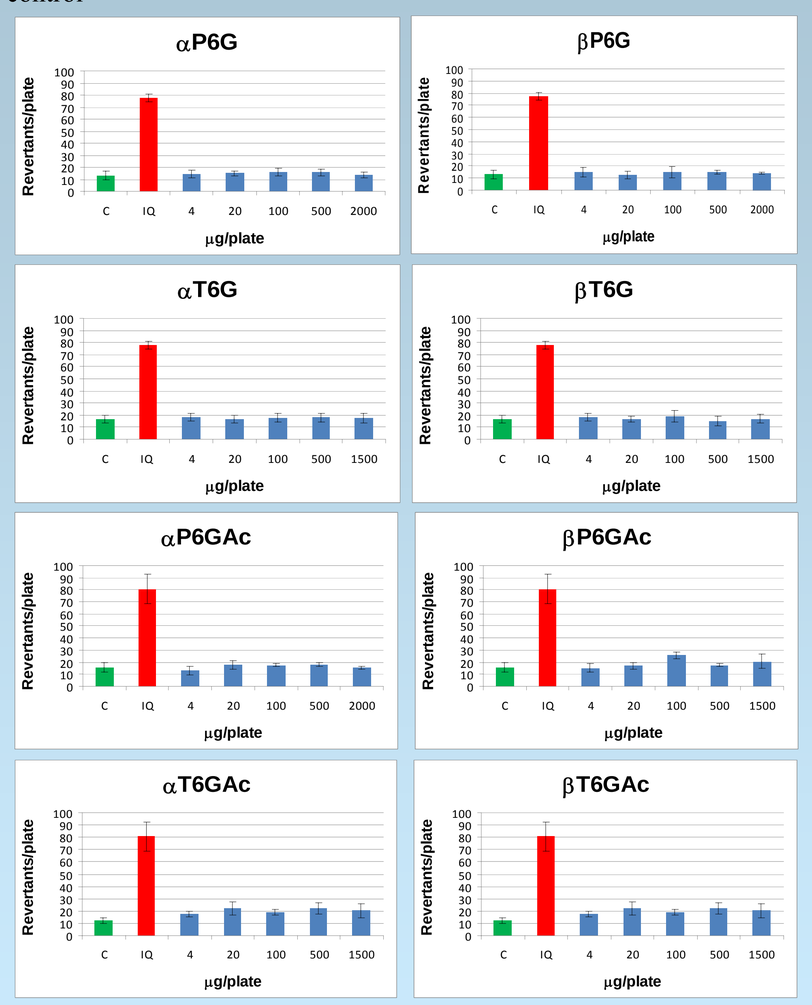
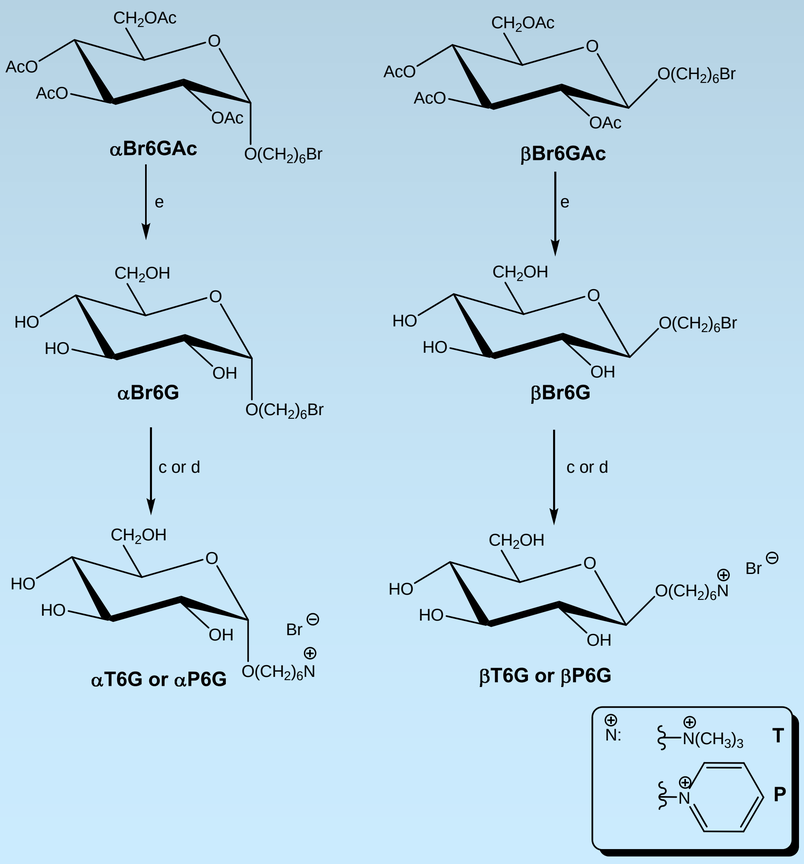



**Table 1.** Chemical shifts of sugar protons (ppm) in the $^1$H NMR spectra

| | H-1 | H-2 | H-3 | H-4 | H-5 | H-6 | H-6' |
|---|---|---|---|---|---|---|---|
| **βBr6GAc** | 4.80; **d,** 1H | 4.97; **dd**, 1H | 5.19; **t**, 1H | 5.07; **t**, 1H | 3.68; **m**, 1H | 4.13; **dd**, 1H | 4.25; **dd**, 1H |
| **αBrG6Ac** | 5.05; **d,** 1H | 4.85; **dd**, 1H | 5.47; **t**, 1H | 5.06; **t**, 1H | 4.00; **m**, 1H | 4.09; **dd**, 1H | 4.27; **dd**, 1H |
| **βT6GAc** | 4.78; **d,** 1H | 4.88; **dd**, 1H | 5.29; **t**, 1H | 5.05; **t**, 1H | 3.99; **m**, 1H | 4.16; **dd**, 1H | 4.32; **dd**, 1H |
| **βP6GAc** | 4.75; **d,** 1H | 4.85; **t**, 1H | 5.28; **t**, 1H | 5.03; **t**, 1H | 3.97; **m**, 1H | 4.15; **dd**, 1H | 4.30; **dd**, 1H |
| **αT6GAc** | 5.12; **d,** 1H | 4.99; **dd**, 1H | 5.38; **t**, 1H | 5.05; **t**, 1H | 4.14; **m**, 1H | 4.15; **dd**, 1H | 4.30; **dd**, 1H |
| **αP6GAc** | 5.10; **d,** 1H | 4.97; **dd**, 1H | 5.36; **t**, 1H | 5.04; **t**, 1H | 4.15; **m**, 1H | 4.13; **dd**, 1H | 4.28; **dd**, 1H |
| **βT6G** | 4.39; **d,** 1H | 3.17; **t**, 1H | 3.42; **t**, 1H | 3.23; **t**, 1H | 3.82; **m**, 1H | 4.65; **m**, 1H | 4.85; **m**, 1H |
| **βP6G** | 4.37; **d,** 1H | 3.18; **t**, 1H | 3.42; **t**, 1H | 3.29; **t**, 1H | 3.72; **m**, 1H | 4.64; **dd**, 1H | 4.84; **dd**, 1H |
| **αT6G** | 4.39; **d,** 1H | 3.49; **dd**, 1H | 3.63; **t**, 1H | 3.34; **t**, 1H | 3.59; **m**, 1H | 3.68; **dd**, 1H | 3.78; **dd**, 1H |
| **αP6G** | 4.82; **d,** 1H | 3.49; **dd**, 1H | 3.61; **m**, 1H | 3.23; **t**, 1H | 3.58; **m**, 1H | 3.68; **dd**, 1H | 3.76; **dd**, 1H |




**Scheme 2:** Reagents and conditions: **c**: $N(CH_3)_3$/EtOH, 70°C, 5h; **d**: Py, 70°C, 24h; **e**: 0.82 M MeONa/MeOH, RT, 24h

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**References:**

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