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**ORIGINAL ARTICLE**

# A general method for the quaternization of N,N-dimethyl benzylamines with long chain n-alkylbromides

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**Summary**
Benzalkonium bromides (BAK) are an important class of cationic surfactants with both industrial and commercial uses. They are used as preservatives for ophthalmic, nasal and parenteral products and they are also used as a topical antiseptic and medical equipment disinfectant. In this work a universal method for the preparation of these compounds is described. Using quaternization of *N,N*-dimethylbenzylamines with long-chain n-alkylbromides we have prepared $C_8$, $C_{10}$, $C_{12}$, $C_{14}$, $C_{16}$, $C_{18}$ and $C_{20}$ homologues of the benzalkonium bromides (BAK).

*Keywords:* benzalkonium bromides – dimethylbenzylamines – n-alkylbromides – alkylating agent – quaternization

## INTRODUCTION

Benzalkonium bromides (BAK) are an important class of cationic surfactants with both industrial and commercial uses. These environmentally friendly antibacterial agents degrade relatively rapidly into non-toxic and inactive products after they have had their desired effect. BAK consists of a mixture of *N*-benzyl-*N,N*-dimethylalkan-1-bromides, which differ in the length of the n-alkyl chain ($C_{12}$, $C_{14}$, $C_{16}$ etc.). Commercially available products contain varying ratios of these components. A very important BAK characteristic is its bactericidal and antimicrobiological properties. The possibilities of BAKs use in medicine are very extensive (Ferrier et al. 2004). The microbiological activity differs in the length of the n-alkyl chain. It is well known that the $C_{12}$-homolog is most effective against yeast and fungi, the $C_{14}$ homologue against gram-positive bacteria and $C_{16}$-homolog against gram-negative bacteria (Merianos 1991). Because of this, they are used as preservatives of ophthalmic, nasal and parenteral products. As well, they are also used as a topical antiseptic and medical equipment disinfectant.

The molecule of the BAK consists of three different moieties: the long alkyl chain ($C_{12}$, $C_{14}$, $C_{16}$ etc.), the short alkyl chain (two times $CH_3$ group) and the benzyl group. Therefore, there exist three synthetic approaches to the preparation of this molecule. All these approaches are described as quaternization of the tertiary amine with the suitable alkylating agent. The first synthetic approach (**I**) consists of the quaternization of the *N,N*-dimethylbezylamine (**1**) with the

n-alkylbromide (**2**) (Zhuravlev et al. 1954, Rudakova and Popova 1966, Moss et al. 1974, Novaki and El Seoud 1999). The second method (**II**) – reaction of the *N,N*-dimethyl-n-alkylamine (**3**) with benzylbromide (**4**) is also commonly used as a method for preparing BAK (Stepanenko et al. 1974, Avram 2001). The reaction of *N*-n-alkyl-*N*-methylbenzylamine (**5**) with methylbromide (**6**) is the last method (**III**) of preparing BAK. Because methylbromide is a gas, this reaction is known in the literature only with methyliodide (Echols et al. 1981). All three methods are shown in Fig 1.

The general procedure for the preparation of BAK using the second above mentioned synthetic approach is described in the literature (Avram 2001). However, the first synthetic approach is not generally used and in every article there are described different conditions of the reaction (Zhuravlev et al. 1954, Rudakova and Popova 1966, Moss et al. 1974, Novaki and El Seoud 1999).

The goal of our work was to describe a simple and easily repeatable method for the synthesis of BAK using the first synthetic approach.

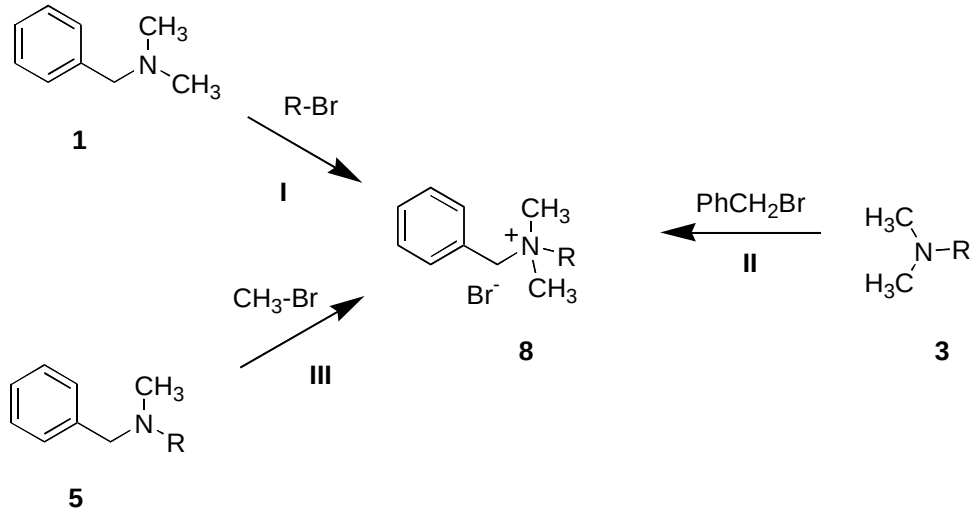


Fig. 1. **Three possible methods of the synthesis of the benzalkonium salts**

## MATERIAL AND METHODS

Melting points were measured on a Boetius block and are uncorrected. The purity of all products was evaluated by HPLC (Spectra Physics instrument equipped with a UV 1000 detector, and Purospher RP-18E column) (Dohnal et al. 2003) and $H^1$-NMR (Varian Gemini 300, 300MHz).

The general preparation procedure is described as follows. The preparation of the *N*-benzyl-*N,N*-dimethyloctan-1-amonium bromide (8a) is shown in Fig. 2. *N,N*-dimethylbenzylamine 1 (1.0g, 0.007mol) in dry ethanol (25ml) was mixed with 1-bromoctane 7 (1.95g, 0.01mol). Mixture was refluxed for 28 hours. After that, solvent was evaporated and the oily residue was purified using column chromatography (Silikagel L 100/250 – VLDU-JEvP, Mobil phase $CHCl_3$:MeOH 100:1). Fractions containing the desired product were collected and evaporated.

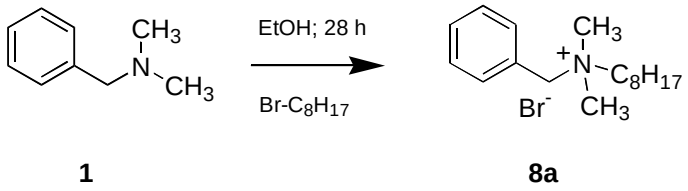


Fig. 2. **Synthesis of the *N*-benzyl-*N,N*-dimethyloctan-1-amonium bromide**

The evaporated crude product – *N*-benzyl-*N,N*-dimethyloctan-1-amonium bromide (8a) was then recrystallized from acetone, washed with ether and allowed to dry. Yield, 0.6g (25%), m.p. 58–60.5°C; $^1$H NMR (300 MHz, DMSO-$d_6$): (8a) – $\delta$0.84 (t, $J$=6.47Hz, 3H, $CH_3$); 1.26 (bs, 10H, $(CH_2)_5$); 1.75 (m, 2H, $CH_2CH_2N^+$); 2.93 (s, 6H, $(CH_3)_2N^+$); 3.23 (t, $J$=6.33Hz, 2H, $CH_2N^+$); 4.54 (s, 2H, $PhCH_2N^+$); 7.51 (bs, 5H, Ph).

Compounds 8b – 8g were prepared using the same method as for the above mentioned compound 8a. Their yields and melting point are shown in Table 1. Their 1H NMR spectra are as follows

*N*-benzyl-*N,N*-dimethyldecan-1-amonium bromide (8b) – $\delta$0.82 (t, $J$=6.60Hz, 3H, $CH_3$); 1.23 (bs, 14H, $(CH_2)_7$); 1.75 (m, 2H, $CH_2CH_2N^+$); 2.93 (s, 6H, $(CH_3)_2N^+$); 3.23 (t, $J$=7.15Hz, 2H, $CH_2N^+$); 4.52 (s, 2H, $PhCH_2N^+$); 7.50 (bs, 5H, Ph).

*N*-benzyl-*N,N*-dimethyldodecan-1-amonium bromide (8c) – $\delta$0.82 (t, $J$=6.60Hz, 3H, $CH_3$); 1.2 (bs, 18H, $(CH_2)_9$); 1.75 (m, 2H, $CH_2CH_2N^+$); 2.94 (s, 6H, $(CH_3)_2N^+$); 3.24 (t, $J$=6.32Hz, 2H, $CH_2N^+$); 4.55 (s, 2H, $PhCH_2N^+$); 7.49 (m, 5H, Ph).

*N*-benzyl-*N,N*-dimethyltetradecan-1-amonium bromide (8d) – $\delta$0.83 (t, $J$=6.60Hz, 3H, $CH_3$); 1.22 (bs, 22H, $(CH_2)_{11}$); 1.75 (m, 2H, $CH_2CH_2N^+$); 2.93 (s, 6H, $(CH_3)_2N^+$); 3.22 (t, $J$=7.71Hz, 2H, $CH_2N^+$); 4.52 (s, 2H, $PhCH_2N^+$); 7.51 (m, 5H, Ph).

*N*-benzyl-*N,N*-dimethyhexadecan-1-amonium bromide (8e) – $\delta$0.82 (t, $J$=6.60Hz, 3H, $CH_3$); 1.21 (bs, 26H, $(CH_2)_{13}$); 1.75 (m, 2H, $CH_2CH_2N^+$); 2.92 (s, 6H, $(CH_3)_2N^+$); 3.21 (t, $J$=8.39 Hz, 2H, $CH_2N^+$); 4.51 (s, 2H, $PhCH_2N^+$); 7.51 (bs, 5H, Ph).

*N*-benzyl-*N,N*-dimethyoctadecan-1-amonium bromide (8f) – $\delta$0.82 (t, $J$=6.47Hz, 3H, $CH_3$); 1.21 (bs, 30H, $(CH_2)_{15}$); 1.75 (m, 2H, $CH_2CH_2N^+$); 2.92 (s, 6H, $(CH_3)_2N^+$); 3.22 (t, $J$=8.25Hz, 2H, $CH_2N^+$); 4.51 (s, 2H, $PhCH_2N^+$); 7.51 (bs, 5H, Ph).

*N*-benzyl-*N,N*-dimethyicosan-1-amonium bromide (8g) – $\delta$0.82 (t, $J$=6.47Hz, 3H, $CH_3$); 1.21 (bs, 34H, $(CH_2)_{17}$); 1.75 (m, 2H, $CH_2CH_2N^+$); 2.93 (s, 6H, $(CH_3)_2N^+$); 3.23 (t, $J$=8.26Hz, 2H, $CH_2N^+$); 4.53 (s, 2H, $PhCH_2N^+$); 7.50 (m, 5H, Ph).

Table 1. **Reaction yields and melting points of the benzalkonium salts**

| Compound | Length of the n-alkyl chain | Yield % | Melting points of the products |
|---|---|---|---|
| 8a | $C_8$ | 25 | 58–60.5°C |
| 8b | $C_{10}$ | 13 | 36–39°C |
| 8c | $C_{12}$ | 41 | 38–43°C |
| 8d | $C_{14}$ | 46 | 46–49°C |
| 8e | $C_{16}$ | 50 | 77–80°C |
| 8f | $C_{18}$ | 71 | 84–88°C |
| 8g | $C_{20}$ | 52 | 86–92°C |

## RESULTS AND DISCUSSION

As mentioned above, the quaternary ammonium compounds (QACs) are widely used industrially and commercially. (McBain et al. 2004). Owing to their extensive use, exact and simple conditions for their preparation should be summarized. Benzalkonium bromides (BAK) are a special part of these compounds. There are three methods of preparing these compounds.

Using our general method we have prepared seven *N*-benzyl-*N,N*-dimethylalkan-1-amonium bromides (n-alkyl – $C_8$, $C_{10}$, $C_{12}$, $C_{14}$, $C_{16}$, $C_{18}$ and $C_{20}$). The preparation approach for all these benzalkonium salts was similar. These compounds differ only in the length of the n-alkyl chain.

All the reaction yields and melting points of the final banzalkonium salts are shown in Table 1. The broader range between the beginning and ending of the melting points is caused by the presence of the long n-alkyl chain in the molecule.

According to our results, we can recommend this synthetic approach for broader use, thanks to its simplicity and the low price of the initial compounds.

In conclusion, we have developed a general method for the preparation of BAK. The melting points of the synthesised bezalkonium salts are

similar to those described in the literature (Zhuravlev et al. 1954, Moss et al. 1974). The reaction yields of the $C_8$ and $C_{10}$ homologues are low – probably thanks to their higher solubility in acetone during the crystallization process. On the other hand, the reaction yields of the $C_{12}$–$C_{20}$ homologues are sufficient and are comparable with those described in the literature (Rudakova and Popova 1966, Moss et al. 1974).

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