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ORIGINAL ARTICLE

SYNTHESIS OF THE ISOQUINOLINIUM SALTS DIFFERING IN THE LENGTH OF THE SIDE ALKYLATING CHAIN

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Summary

Cationic tensides are a widespread group of surface active agents. These compounds have lots of applications in various branches of industry and research. Quaternary isoquinolinium salts differing in alkyl chain length are members of a cationic surfactant group with quaternary nitrogen in its structure. The members of this group can be used as micellar catalysts or disinfectants. Decontamination (chemical warfare agents) or disinfection (bacteria or fungi) for very similar compounds was described several times. In this work, the preparation of isoquinoline-derived cationic surfactants differing in the length of the side alkylating chain from C8 to C20 is described. An HPLC method used for distinction of all prepared long-chain isoquinolinium analogues has been successfully developed.

Key words: isoquinolinium salts; synthesis, HPLC; surfactants; disinfection; decontamination

INTRODUCTION

The 20th century can be appropriately called the age of organic chemistry. It brought many new organic structures, both natural and synthetic. Surfactants are undoubtedly a huge group of organic compounds used technically. These compounds have certainly undergone considerable development since their discovery in 1930. Many applications have been reported for these molecules (detergents, disinfectants, decontamination) [1]. Unfortunately, a dramatic increase in use of these compounds is also reflected negatively on the environment [2]. Surfactants based on quaternary nitrogen have been known for a long time and widely used in various branches (food, pharmaceuticals, textile industry, chemical industry) [3]. Cationic surfactants usually consist of a hydrophilic part represented by quaternary nitrogen moiety and a hydrophobic part represented by

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a long alkyl chain. Similar analogues have been prepared several times, e.g. benzalkonium or cetylpyridinium [4, 5]. The review about synthetic approaches of cationic surfactants was summarized in 1990 by Rosen [6]. Recently, there have been many publications related to the synthesis of double surfactants called "gemini", where two identical parts are coupled into one bisquaternary compound [7, 8]. However, the most useful analogues are still benzalkonium and pyridinium salts [9]. Some of the pyridinium salts have already been used as disinfectants in various technological applications (e.g. component of eye drops, disinfectant solution, disinfectant foam) and their surfactant characteristics (e.g. critical micellar concentration, surface tension) have already been determined and published [10]. Some of the pyridinium salts (C12 and C16) were used to solubilize water-insoluble compounds in analytical chemistry applications, where these can also serve as a qualitative and quantitative tool [11]. Another important feature, already known from the 30´s of the last century, is the ability of cationic surfactants to inhibit growth of some bacteria or fungi. The principle of this effect is their structure similarity with a cell membrane [12]. Many compounds differing in the structure are used as disinfectants. Some of them may be prepared in a monomeric [13], dimeric [14, 15] and also in a polymeric form [16]. Their spermicidal and anti HIV effect has also been reported [17]. A review dealing with the antibacterial effect of cationic surfactants has been published recently by Ressugan [18].

It has been known that these compounds are able to form micelles, which play an important role in a decontamination process [19-21]. These formations are created in a water solution, when the critical micellar concentration (CMC) is exceeded. Therefore, many cationic surfactants work as micellar catalysts, i.e. chemical reactions (decomposition) can be accelerated or inhibited by them [22, 23, 24, 25, 26]. As mentioned above, cationic surfactants are often used to prepare micellar environment for chemical reactions. Recently, a very extensive review on micellar catalysis has been published by Dwars et al. [27].

The aim of this work was to synthesize isoquinolinium salts series with a different alkyl chain length and to confirm their structures by physical-chemical methods. Furthermore, an HPLC method capable of distinquishing members of the whole series was proposed.

METHODOLOGY

The synthesis of several compounds based on quinolinium moiety has been described before [28]. However, there is no description available for a synthesis of the whole series of such salts differing in an alkyl chain (C8 to C20). Formerly, a similar method for preparation of benzalkonium and pyridinium salts was reported by our group [29, 30]. Therefore, a universal method for preparation of monoquaternary isoquinolinium salts with chain substituents was developed. Subsequently, a universal HPLC method for analysing obtained quaternary surfactants was prepared.

Synthesis

A universal method for preparation (Figure 1) of monoquaternary quinolinium salts (**3-9**) was developed as follows: Pure isoquinoline (**1**; 1 eq) in dry ethanol was mixed with 1-bromoalkane (**2**; 14 eq). The mixture was refluxed for 50 hours. The solution was evaporated under reduced pressure and the crude oily product was crystallized from ether, filtered, washed with ether and allowed to dry at r.t.. The reaction process was controlled by TLC (Kieselgel Merck; mobile phase chloroform/methanol 100/1; detection UV 254, Dragendorff reagent).

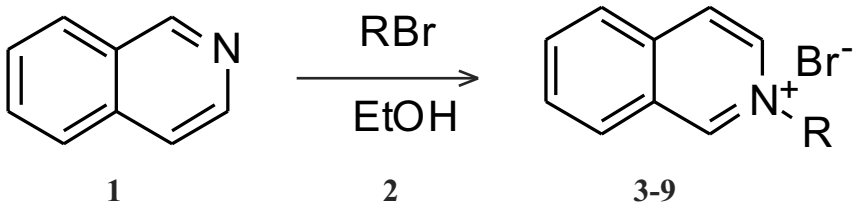

Figure 1. Preparation of isoquinolinium salts. R=C8-C20 (Table 1)

Yields (%), melting points (Boetius, m.p. were uncorrected) are summarized in Table 1. ^{1}H-NMR spectra (Varian Gemini 300, 300 MHz) characterizing each compounds are summarized below:

N-octylisoquinolinium-bromide (**3**)

^{1}H NMR (300 MHz, *DMSO*) ppm 10.25 (s, 1H, ArH), 8.88 (dd, *J* = 6.8, 1.32 Hz, 1H, ArH), 8.62 (d, *J* = 6.8 Hz, 1H, ArH), 8.50 (d, *J* = 8.3 Hz, 1H, ArH), 8.36 (d, *J* = 8.2 Hz, 1H, ArH), 8.24-8.12 (m, *J* = 8.72, 4.95, 1.46 Hz, 1H, ArH), 8.06-7.96 (m, *J* = 7.6Hz, 1H, ArH), 4.74 (t, *J* = 7.4 Hz, 2H, -CH_2-), 1.25-0.94 (m, 12H, -$(CH_2)_6$), 0.80 (t, *J* = 6.7 Hz, 3H, -CH_3)

N-decylisoquinolinium-bromide (**4**)

^{1}H NMR (300 MHz, *DMSO*) ppm 10.23 (s, 1H, ArH), 8.87 (dd, *J* = 6.7 Hz, 1H), ArH) 8.62 (d, *J* = 6.7 Hz, 1H, ArH), 8.50 (d, *J* = 8.2 Hz, 1H, ArH), 8.36 (d, *J* = 8.3 Hz, 1H, ArH), 8.25-8.14 (dd, *J* = 7.9, 7.2 Hz, 1H, ArH), 8.07-7.97 (m, , 1H, ArH), 4.74 (t, *J* = 7.3 Hz, 2H, -CH_2-), 1.41-0.96 (m, 16H, -$(CH_2)_8$-), 0.81 (t, *J* = 6.5 Hz, 3H, -CH_3),

N-dodecylisoquinolinium-bromide (**5**)

^{1}H NMR (300 MHz, *DMSO*) ppm 10.22 (s, 1H, ArH), 8.86 (dd, *J* = 6.7 Hz, 1H), ArH, 8.62 (d, *J* = 6.8 Hz, 1H, ArH), 8.49 (d, *J* = 8.0 Hz, 1H, ArH), 8.36 (d, *J* = 8.2 Hz, 1H, ArH), 8.28-8.21 (m, 1H, ArH), 8.10-8.02 (m, 1H), 4.73 (t, *J* = 7.3 Hz, 2H, -CH_2-), 1.36-1.08 (m, 20H, -$(CH_2)_{10}$-), 0.82 (t, *J* = 6.66 Hz, 3H, -CH_3)

N-tetradecylisoquinolinium-bromide (**6**)

^{1}H NMR (300 MHz, DMSO) ppm 10.20 (s, 1H, ArH), 8.85 (dd, *J* = 6.7 Hz, 1H, ArH), 8.62 (d, *J* = 6.7 Hz, 1H, ArH), 8.49 (d, *J* = 8.2 Hz, 1H, ArH), 8.36 (d, *J* = 8.2 Hz, 1H, ArH), 8.28-8.21 (m, 1H, ArH), 8.12-8.02 (m, 1H, ArH), 4.73 (t, *J* = 7.3 Hz, 2H, -CH_2-), 1.37-1.08 (m, 24H, -$(CH_2)_{12}$-), 0.82 (t, *J* = 6.6 Hz, 3H, -CH_3)

N-hexadecylisoquinolinium-bromide (**7**)

^{1}H NMR (300 MHz, *DMSO*) ppm 10.25 (s, 1H, ArH), 8.87 (dd, *J* = 6.8 Hz, 1H, ArH), 8.63 (d, *J* = 6.7 Hz, 1H, ArH), 8.50 (d, *J* = 8.1 Hz, 1H, ArH), 8.36 (d, *J* = 8.3 Hz, 1H, ArH), 8.25-8.19 (m, *J* = 7.6 Hz, 1H, ArH), 8.12-8.03 (m, 1H, ArH), 4.74 (t, *J* = 7.3 Hz, 2H, -CH_2-), 1.38-1.08 (m, 28H, -$(CH_2)_{14}$-), 0.81 (t, *J* = 6.6 Hz, 3H, -CH_3)

N-octadecylisoquinoliniumbromide (**8**)

^{1}H NMR (300 MHz, *DMSO*) ppm 10.20 (s, 1H, ArH), 8.85 (dd, *J* = 6.8 Hz, 1H, ArH), 8.61 (d, *J* = 6.7 Hz, 1H, ArH), 8.49 (d, *J* = 8.3 Hz, 1H, ArH), 8.36 (d, *J* = 8.3 Hz, 1H, ArH), 8.25-8.20 (m, *J* = 7.63 Hz, 1H, ArH), 8.08-8.02 (m, 1H, ArH), 4.72 (t, *J* = 7.2 Hz, 2H, -CH_2-), 1.24-1.07 (m, 32H, -$(CH_2)_{16}$-), 0.82 (t, *J* = 6.08 Hz, 3H, -CH_3)

N-eicosylisoquinoliniumbromide (**9**)

^{1}H NMR (300 MHz, *DMSO*) ppm 10.18 (s, 1H, ArH), 8.89 (dd, *J* = 6.8 Hz, 1H, ArH), 8.61 (d, *J* = 6.7 Hz, 1H, arH), 8.49 (d, *J* = 8.30 Hz, 1H, ArH), 8.36 (d, *J* = 8.20 Hz, 1H, ArH), 8.27-8.22 (m, 1H, ArH), 8.08-8.03 (m, 1H, ArH), 4.72 (t, *J* = 7.3 Hz, 2H, -CH_2-), 1.20-1.09 (m, 36H, -$(CH_2)_{18}$-), 0.82 (t, *J* = 6.6 Hz, 3H, -CH_3)

HPLC Analysis

After preparation of the isoquinolinium salts, an appropriate HPLC method for their distinction in the mixture was developed. The HPLC system consisted of a P200 gradient pump (Spectra-Physics Analytical, Fremont, USA), a 7125 injection valve – 10 µl loop (Rheodyne, Cotati, USA), an UV1000 detector (Spectra-Physics Analytical, Fremont, USA), and a CSW Chromatography Station 1.5 software (DataApex, Prague, Czech Republic). A 250×4 mm I.D. Waters Spherisorb Cyano (5 µm) column was used (Supelco Inc., Bellefonte, USA) for analyses. The mobile phase consisted of 45 % acetonitrile and 55 % water. This mixture was prepared as a 0.1 M sodium acetate solution. Finally, the pH was adjusted with acetic acid to 5.0. The samples were delivered isocratically at a flow-rate of 1 ml/min. The absorbance was measured at 257 nm.

RESULTS AND DISCUSSION

Synthesis and HPLC analysis

The results obtained with the prepared compounds are shown in Table 1 (yields, melting points and HPLC retention times). Apparently, the preparation of isoquinolinium salts with side chains C8-C20 seems to be relatively easy, but the purification process to reach satisfying purity was rather difficult. The yields are relatively high and very similar to the previously prepared compounds derived from *N,N*-dimethyl-*N*-benzylamine or pyridine [29, 30]. We suppose that the larger nucleophilic moiety (isoquinoline) has no negative steric effect as it is expected for e.g. quinoline. The probability of the nucleophilic attack is almost

the same as for the pyridine. In general, we have obtained the amount of white crystals of the desired compound from the reaction. Reaction products were detected using the TLC method. The satisfactory purity was usually reached after one or two crystallizations from ether suspension. On the other hand, the compounds with the alkyl length C8 and C20 had to be crystallized several times to get the sufficient purity, however the yields decreased rapidly in this case. It was observed that yields decreased with the increasing alkyl length except C8 and C10. The compounds with the chain length of C8 and C10 were difficult to convert into crystals due to their low melting point.

Table 1. Yields, melting points and retention times of prepared quinolinium salts.

Compound	Side alkylating chain (R)	Yield (%)	m.p. (C°)	HPLC Rt (min)
3	C8	91	46-48	5.36
4	C10	78	40-42	6.18
5	C12	69	58-60	7.12
6	C14	87	60-62	8.20
7	C16	84	68-70	9.46
8	C18	84	76-78	10.96
9	C20	53	81-83	12.82

Additionally, the HPLC method for product obtained in this study was developed. It allows distinguishing all prepared quaternary isoquinolinium salts (Figure 2). The shortest retention time was found for the C8 isoquinolinium salt. It is supposed that this novel HPLC assessment could be easily used for characterization of mixtures of related isoquinolinium compounds.

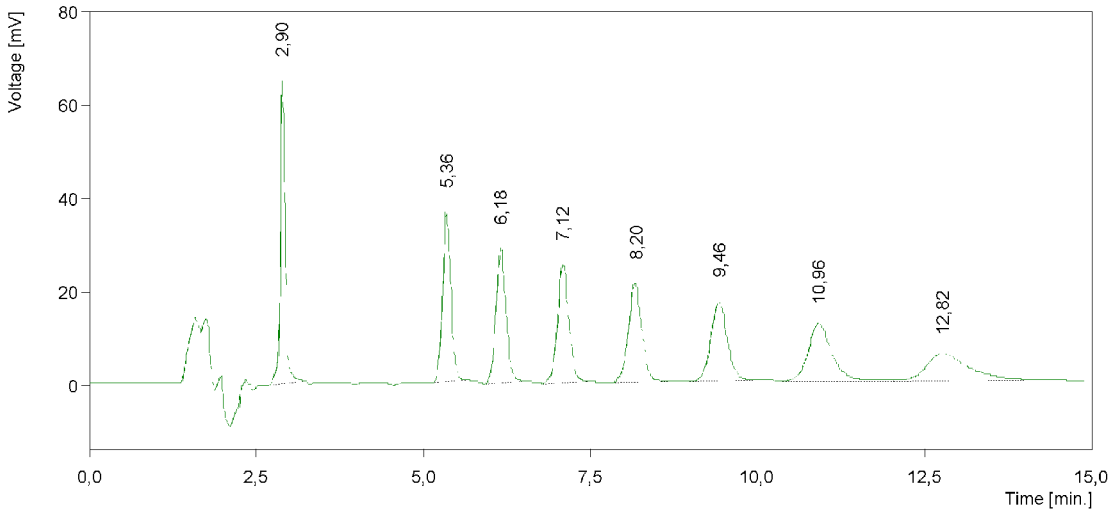

Figure 2. HPLC chromatogram of isoquinolinium compounds mixture.

CONCLUSIONS

In conclusion, the synthetic protocol for a fast preparation of isoquinolinium salts was developed. The whole set including seven members of cationic surfactants based on isoquinolinium moiety was prepared. The structures were confirmed by an analytical method (NMR). In a larger consequence, an HPLC experimental protocol was developed for estimation of quaternary detergent purity and for their resolution in a mixture.

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