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Synthesis and Spectral Analysis of Pyridine Derivates

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Abstract. The present study described a detailed investigation of the synthesis of novel quaternary pyridinium salts: derivates of 1-(3-pyridine)undecane-1-one (1-propyl-3-undecanoylpyridinium bromide and 1-propyl-3-undecanoylpyridinium chloride) and *N*-decyloxypyridine-3-carboximidamide (3-[1-(N-decyloxyimine)ethyl]-1-propylpyridinium chloride and 3-[1-(N-decyloxyimine)ethyl]-1-propylpyridinium bromide). The structures of the products were confirmed by spectral(^{1}H-NMR, ^{13}C-NMR, FT-IR) analysis, mass spectrometry methods. Estimation of the pharmacotherapeutic potential has been accomplished for synthesized compounds on the basis of Prediction of Activity Spectra for Substances (PASS programe).

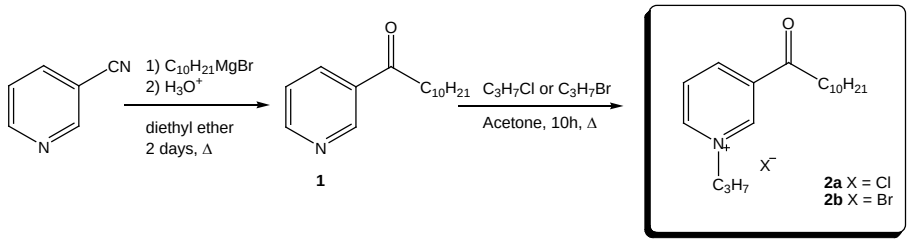
Keywords: Quaternary pyridinium salts, synthesis, quarterisation reaction, *O*-alkylation, prediction of activity

1 Introduction

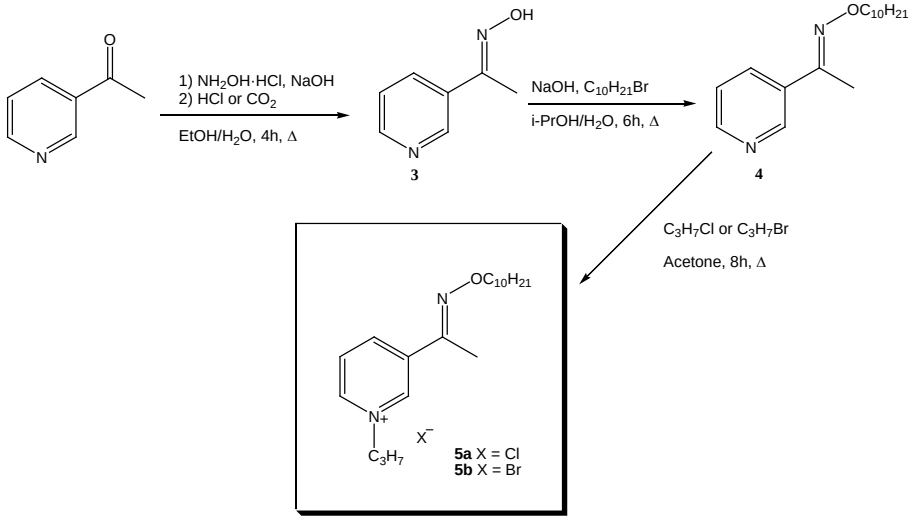
First reports about quaternary ammonium salts appeared in 1890, when Menchutkin first time conducted reaction of a tertiary amine with an alkyl halide [1]. The Menchutkin reactions (MR) with the exception of a few cases, are of the S_N2 type. Primary halides are generally more reactive than secondary or tertiary halides [2], reactivity increase in the order: iodide > bromide > chloride [3-5]. The MR needs an appropriate polar solvent (such as alcohol, aceton etc.). In a strongly polar medium the reaction takes place more easily through the stabilization of the transition state and the charged products, which are more polar than the reactants.

From that time many studies of quaternary ammonium salts, were carried out what brought huge knowledge about their properties and utility. Those properties are used in many areas of our daily lives [6]. They are used as catalysts, substrates for ionic liquids synthesis, in textile industry or even as wood impregnation agents [7-9]. Moreover they may be used in cosmetics industries [10,11], nanomaterials synthesis or pharmaceuticals [12,13]. Besides they have biological active properties, which is the reason why they are very often used as bactericidals, fungicidals [13] and also as herbicides [6,14-19]. Pyridine oximes and their quaternary salts are also used as selective and efficient extractants in metals recovery from aqueous solution [20,21].

Therefore, the goal of the research was to synthesize novel quaternary pyridinium salts: derivates of 1-(3-pyridine)undecane-1-one and *N*-decyloxypyridine-3-carboximidamide in large scale and with high yields. In this work, two starting compounds were proposed: the two-step synthesis of quaternary salts of 1-(3-pyridine)undecane-1-one (Scheme 1.) and the three-step synthesis of quaternary salts of *N*-decyloxypyridine-3-carboximidamide (Scheme 2). Both of these methods can be also used to synthesize substituent at position 2 and 4 of the pyridine ring.



Scheme 1. Two-step synthesis of 1-propyl-3-undecanoylpyridinium bromide and 1-propyl-3-undecanoylpyridinium chloride (2a-b).



Scheme 2. Three-step synthesis of 3-[1-(*N*-decyloxyimine)ethyl]-1-propylpyridinium chloride and 3-[1-(*N*-decyloxyimine)ethyl]-1-propylpyridinium bromide (5a-b).

2 Results and Discussion

1-propyl-3-undecanoylpyridinium chloride (2a) and 1-propyl-3-undecanoylpyridinium chloride (2b) were synthesized using the two-step synthesis. In the first case, using the two-step synthesis, only derivatives of the 2-position of the pyridine ring were synthesized. In the first step mixture was heated under reflux and under anhydrous conditions for seven hours (solution is decolorized, it means the start of reaction). In the next step, during the addition of 3-cyanopyridine solution color changes from green to orange. After that, solution was neutralized by adding stoichiometric amount of aqueous solution of saturated ammonium chloride hydrochloric acid and sodium hydroxide until pH reached neutral. The resulting two layers can be easily separated and purified using chloroform, washed with brine and dried. The crude product obtained was chromatographed on a column of silica gel. The second step was a substitution reaction (S_N2) with an appropriate halide in anhydrous acetone. The results of the reaction were summarized in Table 1.

Table 1. Yields and forms of synthesized derivates of of 1-(3-pyridine)undecane-1-one

No	Yield [%]	Form
1	89.5	solid (43.0 - 43.2°C)
2a	83.2	solid (40.3 - 41.0°C)
2b	92.4	solid (39.0 - 40.0°C)

Quaternary salts derivates of *N*-decyloxypyridine-3-carboximidamide were obtained by the oximation reaction of the 3-acetylpyridine with hydroxylamine hydrochloride in the presence of NaOH (at pH = 7; ethanol-water mixture 4:1 (v/v)). The second step was the reaction of quaternization of obtained oxime. The last step was a quaternization reaction with an appropriate halide in anhydrous acetone. Products form and yields were summarized in Table 2.

Table 2. Yields and characteristic spectral data of synthesized derivates of *N*-decyloxypyridine-3-carboximidamide

No	Yield [%]	Form
3	97	solid (103°C)
4	98	oil
5a	92	oil
5b	95	oil

The potential pharmacological activities of the synthesized compounds have been also studied. A computer-aided drug discovery approach with the *in silico* Prediction of Activity Spectra for Substances (PASSs) program was used. The PASS software is useful for the study of biological activity of organic compounds. A few types of activities were predicted for a potential compound with the highest probability. If predicted activity (PA) > 0.8, the substance is very likely to exhibit experimental activity and the chance of the substance being the analogue of a known pharmaceutical agent is also high. According to data from PASS program the most frequently predicted types of biological activity are: carboxypeptidase Taq inhibitor and pullulanase inhibitor.

Table 3. Probability "to be Active" (PA) values for predicted biological activity of compounds 1, 2a-b.

Focal predicted activity (PA > 0.80)	Compound		
	1	**2a**	**2b**
Carboxypeptidase Taq inhibitor	0.898	0.853	0.870
Pullulanase inhibitor	0.875	0.808	0.878
CYP2F1 substrate	0.873	-	-
Taurine dehydrogenase inhibitor	0.873	-	-
Pro-opiomelanocortin converting enzyme inhibitor	0.856	-	0.809
Superoxide dismutase inhibitor	0.842	-	-
Amine dehydrogenase inhibitor	0.818	-	-
Gluconate 5-dehydrogenase inhibitor	-	-	0.817
Maleate isomerase inhibitor	-	-	0.801

Table 4. Probability "to be Active" (PA) values for predicted biological activity of compounds 3,4 and 5a-b.

Focal predicted activity (PA > 0.80)	Compound			
	3	**4**	**5a**	**5b**
Muramoyltetrapeptide carboxypeptidase inhibitor	0.892	0.846	-	-
3-Hydroxybenzoate 4-monooxygenase inhibitor	0.830	-	-	-
Dehydro-L-gulonate decarboxylase inhibitor	0.832	-	-	-
Fragilysin inhibitor	0.828	-	-	-
Nicotinamidase inhibitor	0.810	-	-	-
Carboxypeptidase Taq inhibitor	0.808	0.849	0.836	0.855
Phobic disorders treatment	-	0.947	-	0.887
Sugar-phosphatase inhibitor	-	0.882	-	-
Pullulanase inhibitor	-	0.832	0.872	0.839
Gluconate 5-dehydrogenase inhibitor	-	0.829	-	-

3 Experimental

3.1 Material and Methods

Melting points were determined using a Boetius hot stage apparatus. The nuclear magnetic resonance (NMR) spectra were measured with a Bruker Avance II 400 MHz UltraShield Plus spectrometer, operating at 400.6 and 101.2 MHz for ^{1}H and ^{13}C, respectively. The number of scans varied from 1000 to 5,000 per spectrum. The ^{13}C and ^{1}H chemical shifts were measured in $CDCl_3$ or DMSO-d6 relative to an internal standard of TMS. Infrared spectra were recorded in the KBr pellets or solutions in chloroform using Vertex 70, Bruker Optics spectrophotometer. The ESI (electron spray ionization) mass spectra were recorded on API 4000 QTRAP, AB Sciex (Foster City, CA, USA) spectrometer. The sample solutions were prepared in methanol at the concentration of approximately 10^{-5} M. The standard ESI-MS mass spectra were recorded at the cone voltage 30 V. The low- and high-resolution mass spectra were recorded on an Intectra Mass AMD 402 (ionization method EI, 70 eV) spectrometer. Reaction progress and purity of the compounds were monitored by thin-layer chromatography(TLC) using precoated aluminum-backed silica plates (E. Merck, DC-60F_{254}) and monitored by UV lamp (UV 254 nm). Silica gel 60 (E. Merck 70–230 mesh) was used for column chromatography.

3.2 Typical Procedure for the Preparation of *Quaternary Salts of 1-(3-Pyridine) Undecane-1-One* by Two-Step Method

3.2.1 Synthesis of *1-(3-pyridine)undecane-1-*one (1)

In round bottom flask, 0.2 mol (4.86 g) dried magnesium (POCH) and a crystal of iodine was placed. Then solution of 0.25 mol (42.75 g) of decyl bromide (Sigma Aldrich) in 300 ml dry diethyl ether (POCH) was slowly added. The mixture was stirred under reflux for six hours. After that 0.2 mol pyridine-3-carbonitrile (Sigma Aldrich) was added and heated under reflux for 7 hours. The solution was neutralized by adding stoichiometric amount of aqueous solution of saturated ammonium chloride(POCH), next 15% hydrochloric acid (15%, POCH) and sodium hydroxide (20%, POCH). Then the resulting aqueous solution was extracted using chloroform, washed with brine and dried with anhydrous $MgSO_4$. The crude product was chromatographed on silica gel (200 g) with toluene-chloroform 5:1 (v/v) as an eluent.

1-(3-pyridine)undecane-1-one (1) Rf=0.61 (chloroform-heptane 1:1).

3.2.2 Synthesis of *1-propyl-3-undecanoylpyridinium bromide and chloride* (2a-b)

In round bottom flask, 0.1 mol (13.62 g) of *1-(3-pyridine)undecane-1-one* and 0.125 mol propyl bromide or chloride (15.25 g/9.82 g) (Sigma Aldrich) was dissolved in 100 ml of dry acetone and warm up to 40°C. Then mixture was filtered and concentrated under rotary evaporator. The crude product was recrystallized from acetone.

1-propyl-3-undecanoylpyridinium bromide (2a) Rf=0.46 (chloroform-heptane 1:1)

1-propyl-3-undecanoylpyridinium chloride (2b) Rf=0.42 (chloroform-heptane 1:1)

3.3 Typical procedure for the preparation of *quaternary salts of N-decyloxypyridine-3-carboximidamide* by three-step method

3.3.1 Synthesis of *1-(3-pyridine)ethane-1-one oxime* (3)

In round bottom flask, 0.25 mol of hydroxylamine hydrochloride (17.4 g) (POCH) and 0.2 mol sodium hydroxide (8.0 g) (POCH) was dissolved in 300 ml of an ethanol-water mixture 4:1 (v/v) and warm up to 50°C, after that 3-acetylpyridine (Sigma Aldrich) was added to the reaction mixture and heated under reflux by 4 h. After that, hydrochloric acid or dry ice was added, to precipitate the product. The white powder was recrystallized from water. The spectroscopic parameters of 1-(3-pyridine)ethane-1-one oxime (FT-IR, ^{1}H-NMR, and ^{13}C-NMR) were identical to those given in the literature. Mp. 103°C.

1-(3-pyridine)ethane-1-one oxime (3) Rf=0.54 (chloroform: heptane 1:1).

3.3.2 Synthesis of *N-decyloxypyridine-3-carboximidamide* (4)

In round bottom flask, 0.25 mol of 1-(3-pyridine)ethane-1-one oxime (17.4 g)and 0.2 mol sodium hydroxide (8.0 g) (POCH) was dissolved in 300 ml of an isopropyl-water mixture 5:1 (v/v) and warm up

to 50°C, after that decyl bromide (Sigma Aldrich) was added to the reaction mixture and heated under reflux by 6 h. After that, hydrochloric acid or dry ice was added, to precipitate the product. The crude product was chromatographed on silica gel (200 g) with toluene-chloroform 6:1 (v/v) as an eluent.

N-decyloxypyridine-3-carboximidamide (4) Rf=0.63 (toluene-chloroform 1:1).

3.3.3 Synthesis of 3-[1-(*N*-decyloxyimine)ethyl]-1-propylpyridinium chloride and bromide(5a-b)

In round bottom flask, 0.1 mol (27.64 g) of *N*-decyloxypyridine-3-carboximidamide and 0.125 mol propyl bromide or chloride (15.25 g/ 9.82 g) (Sigma Aldrich) was dissolved in 100 ml of dry acetone and warm up to 40°C. Then mixture was filtered and concentrated under rotary evaporator. The crude product was recrystallized from acetone.

3-[1-(N-decyloxyimine)ethyl]-1-propylpyridinium chloride (5a) Rf=0.52 (toluene-chloroform 1:1).

3-[1-(N-decyloxyimine)ethyl]-1-propylpyridinium bromide (5b) Rf=0.50 (toluene-chloroform 1:1).

1-(3-pyridine)undecane-1-one (1)- FT-IR [cm^{-1}]: 2890; 1690; 1730; 1450; ^{1}H NMR ($CDCl_3$,DMSO) δ in ppm: 9.15 (Py-2, 1H, s); 8.75 (Py-6, 1H, dd, J_1= 3.17 Hz, J_2= 6.36 Hz); 8,23 (Py-4, 1H, dd, J_1=3.18 Hz, J_2= 12.47 Hz); 7.4 (Py-5, 1H, t); 2.96 (2H, t); 1.73 (2H, qw); 1.37-1.24 (14H, m); 0.86 (3H, t); ^{13}C NMR ($CDCl_3$,) δ in ppm: 198.7 (C=O); 152.8 (Py-2); 149.1 (Py-6); 134.8 (Py-4); 131.7 (Py-3); 123.0 (Py-5); 39.1; 38.4; 37.4; 35.2; 31.3; 29.0; 28.8; 23.5; 22.1; 13.6; (ESI-MS) m/z: 247.38 $(M+H)^+$; HRMS (EI): Calcd for $C_{16}H_{25}NO$ $(M)^+$: m/z 247.1936. Found: m/z 247.1935. Rf=0.61 (chloroform-heptane 1:1).

1-propyl-3-undecanoylpyridinium bromide (2a)- FT-IR [cm^{-1}]: 2890; 1680; 1735; 1450; 860; ^{1}H NMR ($CDCl_3$,DMSO) δ in ppm: 9.20 (Py-2, 1H, s); 8.60 (Py-6, 1H, dd, J_1= 3.16 Hz, J_2= 6.34 Hz); 8,20 (Py-4, 1H, dd, J_1= 3.16 Hz, J_2= 12.30 Hz); 7.45 (Py-5, 1H, t); 3.66 (N-CH_2; 2H,t); 2.96 (2H, t); 1.75 (2H, qw); 1.36-1.23 (18H, m); 0.83 (6H, t); ^{13}C NMR ($CDCl_3$,) δ in ppm: 200.1 (C=O); 148.1 (Py-2); 146.0 (Py-6); 145.6 (Py-4); 141.2 (Py-3); 137.6 (Py-5); 64.3; 38.4; 29.6; 29.4; 29.0; 25.6; 22.7; 14.1; 12.5;(ESI-MS) m/z: 370.37 $(M+H)^+$; HRMS (EI): Calcd for $C_{19}H_{32}BrNO$ $(M)^+$: m/z 369.1167. Found: m/z 369.1168. Rf=0.46 (chloroform-heptane 1:1).

1-propyl-3-undecanoylpyridinium chloride (2b)- FT-IR [cm^{-1}]: 2890; 1725; 1680; 1450; 770; ^{1}H NMR ($CDCl_3$,DMSO) δ in ppm: 9.22 (Py-2, 1H, s); 8.70 (Py-6, 1H, dd, J_1= 3.16 Hz, J_2= 6.24 Hz); 8,30 (Py-4, 1H, dd, J_1= 3.16 Hz, J_2= 12.50 Hz); 7.45 (Py-5, 1H, t); 3.50 (N-CH_2; 2H,t); 2.96 (2H, t); 1.73 (2H, qw); 1.36-1.24 (18H, m); 0.86 (6H, t); ^{13}C NMR ($CDCl_3$,) δ in ppm: 200.1 (C=O); 148.1 (Py-2); 145.6 (Py-6); 137.6 (Py-4); 132.3 (Py-3); 128.4 (Py-5); 64.3; 38.4; 31.9; 29.7; 29.4; 29.2; 25.6; 22.8; 14.1; 12.5; (ESI-MS) m/z: 325.92 $(M+H)^+$; HRMS (EI): Calcd for $C_{19}H_{32}ClNO$ $(M)^+$: m/z 325.2172. Found: m/z 325.2175. Rf=0.42 (chloroform-heptane 1:1).

1-(3-pyridine)ethane-1-one oxime (3) - FT-IR [cm^{-1}]:3600; 2965; 1686; 1435; 1100; ^{1}H NMR ($CDCl_3$,DMSO) δ in ppm: 9.10 (O-H, 1H, s); 8,84 (Py-2, 1H, s); 8.50 (Py-6, 1H, d); 7.82 (Py-5, 1H, t); 7.22 (Py-4, 1H, d); 0.84 (3H, t); ^{13}C NMR ($CDCl_3$,) δ in ppm: 150.0 (Py-2); 148.2 (Py-6); 147.5 (Py-4); 133.2 (Py-3); 132.4 (Py-5); 121.6 (C=N); 13.7; ^{13}C NMR ($CDCl_3$,) δ in ppm: (ESI-MS) m/z: 135.16 $(M+H)^+$; HRMS (EI): Calcd for $C_7H_8N_2O$ $(M)^+$: m/z 136.0637. Found: m/z 136.0636. Rf=0.54 (chloroform: heptane 1:1).

N-decyloxypyridine-3-carboximidamide (4) - FT-IR [cm^{-1}]: 3200; 2986; 1678; 1450; 1020; ^{1}H NMR ($CDCl_3$,DMSO) δ in ppm: 8,85 (Py-2, 1H, s); 8.55 (Py-6, 1H, d); 7.94 (Py-5, 1H, t); 7.23 (Py-4, 1H, d); 4.18 (O-CH_2; 2H,t); 2.21 (3H, s); 1.87 (2H, m); 1.25 (14H, m); 0.85 (3H, t); ^{13}C NMR ($CDCl_3$,) δ in ppm: 150.1 (Py-2); 149.2 (Py-6); 146.8 (Py-4); 132.6 (Py-3); 132.0 (Py-5); 121.6 (C=N); 74.10; 31.4; 29.6; 29.0; 28.8; 27.4; 25.5; 25.2; 22.1; 13.7; 11.7; (ESI-MS) m/z: 276.42 $(M+H)^+$; HRMS (EI): Calcd for $C_{17}H_{28}N_2O$ $(M)^+$: m/z 276.2202. Found: m/z 276.2204. Rf=0.63 (toluene-chloroform 1:1).

3-[1-(N-decyloxyimine)ethyl]-1-propylpyridinium chloride (5a) - FT-IR [cm^{-1}]:3100; 2985; 1650; 1465; 1000; 760; ^{1}H NMR ($CDCl_3$,DMSO) δ in ppm: 8,80 (Py-2, 1H, s); 8.53 (Py-6, 1H, d); 7.90 (Py-5, 1H, t); 7.24 (Py-4, 1H, d); 4.34 (O-CH_2; 2H,t); 3.78 (N-CH_2, 2H,t); 2.25 (3H, s); 1.80 (2H, m); 1.24 (16H, m); 0.86 (6H, t); ^{13}C NMR ($CDCl_3$,) δ in ppm: 150.5 (Py-2); 148.2 (Py-6); 147.8 (Py-4); 135.6 (Py-3); 132.5 (Py-5); 121.8 (C=N); 74.10; 64.78; 31.4; 30.8; 29.6; 29.4; 29.0; 28.8; 27.4; 25.5; 25.2; 22.1; 13.7; 11.7; ^{13}C NMR ($CDCl_3$,) δ in ppm: (ESI-MS) m/z: 354.96 $(M+H)^+$; HRMS (EI): Calcd for $C_{20}H_{35}ClN_2O$ $(M)^+$: m/z 354.2438. Found: m/z 354.2441. Rf=0.52 (toluene-chloroform 1:1).

3-[1-(N-decyloxyimine)ethyl]-1-propylpyridinium bromide (5b) - FT-IR [cm^{-1}]:3200; 2984; 1670; 1540; 1460; 1010; 880; ^{1}H NMR ($CDCl_3$,DMSO) δ in ppm: 8,85 (Py-2, 1H, s); 8.55 (Py-6, 1H, d); 7.95 (Py-5, 1H, t); 7.22 (Py-4, 1H, d); 4.44 (O-CH_2; 2H,t); 3.83 (N-CH_2, 2H,t); 2.25 (3H, s); 1.85 (2H, m); 1.24 (16H, m); 0.85 (6H, t); ^{13}C NMR ($CDCl_3$,) δ in ppm: 151.5 (Py-2); 148.4 (Py-6); 147.0 (Py-4); 135.4 (Py-3);

132.2 (Py-5); 121.7 (C=N); 75.1; 64.7; 32.4; 30.9; 29.8; 29.6; 29.2; 28.8; 27.5; 25.4; 25.2; 22.1; 13.0; 11.2; (ESI-MS) m/z: 399.41 $(M+H)^+$; HRMS (EI): Calcd for $C_{20}H_{35}BrN_2O$ $(M)^+$: m/z 398.1933. Found: m/z 398.1931. Rf=0.50 (toluene-chloroform 1:1).

4 Conclusion

The efficient two- and three-step procedure for new quaternary pyridinium salts (1-propyl-3-undecanoylpyridinium bromide, 1-propyl-3-undecanoylpyridinium chloride, synthesis on a large scale were developed. These new compounds were characterized by spectroscopic methods and may find applications in pharmacology.

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