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N-TOSYLCARBAMIDE DERIVATIVES OF 2-PYRIDINIUM AND 2-PYRIMIDINIUM – A NEW CLASS OF INHIBITORS OF METABOLICALLY EXCITABLE POTASSIUM CHANNELS IN CELLS OF THE MYOCARDIUM

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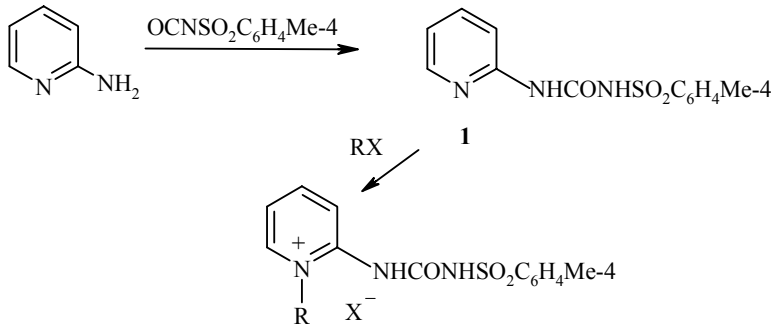
Inhibitors are the most important among modulators of the potassium channels of cells – derivatives of sulfonylureas or thioureas [1]. While compounds of similar type, for example *glibenclamide*, have been used with success in the treatment of diabetes, the search for agents for correction of the potassium current in cells of the heart is still continuing, since they are very important for heart failure, arrhythmia, etc. The majority of derivatives of sulfonylureas inhibit potassium channels of the ventricles of the heart and have almost no effect on the atria. Imitating the structure of acetylcholine (or muscarine), we have succeeded in preparing the N-tosylcarbamide derivatives of 2-pyridinium **1a,b** and 2-pyrimidinium **2a,b** which strongly inhibit the potassium acetycholinic channels (K_{Ach}) of the atria of the porpoise. The effectiveness of the compounds synthesized was determined by a previously described method [2]. We note that derivatives containing a heterocyclic nitrogen quaternized with a methyl or 4-nitrobenzyl group, exceptionally strongly the contractibility of the myocardium and the duration of the potential effect.

The 2-pyridinium N-tosylcarbamides **1a,b** were prepared as follows:



1a,**b**

1 a R = $CH_2C_6H_4NO_2$-4, **b** R = Me, **a** X = Br, **b** X = I

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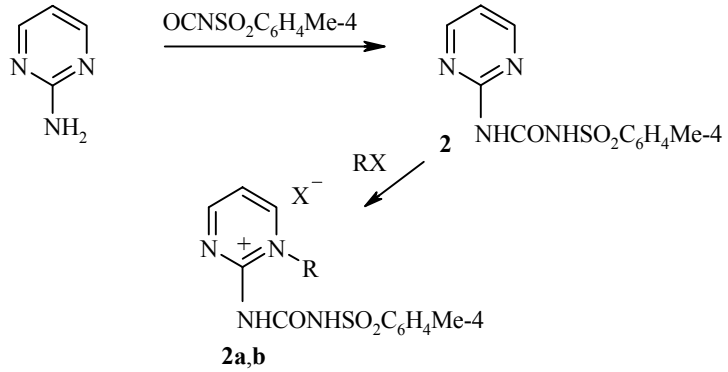
The 2-pyrimidinium salts **2a,b** were prepared analogously.



2 a R = $CH_2C_6H_4NO_2$-4, **b** R = Me, **a** X = Br, **b** X = I

^{1}H NMR spectra of DMSO-d_6 solutions with HMDS as internal standard were recorded with Bruker AC 250-P (250 MHz) instrument. The course of reactions and the purity of the products were monitored by TLC on Silufol UV-254 strips with 8:4:1:3 butan-1-ol–ethanol–acetic acid–water as eluant and revelation of the spots with iodine vapor.

1-[4-(Methylphenyl)sulfonyl]-3-pyridin-2-yl)urea (1), mp 154-155°C, and **1-[4-(Methylphenyl)sulfonyl]-3-(pyrimidin-2-yl)urea (2)**, mp >250°C, were prepared by method [3].

2-[(4-Methylphenyl)sulfonylcarbamido]-1-(4-nitrobenzyl)pyridinium Bromide (1a). 4-Nitrobenzyl bromide (2.16 g 10 mmol) was added to a solution of compound **1** (2.91 g, 10 mmol) in 2-butanone (15 ml) and the mixture was heated at 90°C for 3 h, cooled, the precipitate was separated, washed with 2-butanone and recrystallized from ethanol; mp > 250°C (dec.), R_f 0.52. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.51-8.52 (2H, s, 2NH); 8.30-8.26 (2H, m, ArH); 8.18 (2H, d, *J* = 8.7, ArH); 8.99 (1H, dt, *J* = 1.5, *J* = 6.9, ArH); 7.49 (2H, d, *J* = 8.7, ArH); 7.23 (1H, dt, *J* = 1.5, *J* = 6.9); 5.72 (2H, s CH_2), 3.38 (3H, s, CH_3). Found, %: C 47.07; H 3.49; Br 15.52; N 10.81; S 6.09. $C_{20}H_{19}BrN_4O_5S$. Calculated, %: C 47.30; H 3.74; Br 15.77; N 11.04; S 6.31.

1-Methyl-2-[(4-methylphenyl)sulfonylcarbamido]pyridinium Iodide (1b) was prepared analogously to **1a** from compound **1** (2.91 g, 10 mmol) in 2-butanone and methyl iodide (1.42 g, 10 mmol) after heating at 70°C for 1.5 h and cooling, the crystal substance was filtered off and washed with 2-butanone to give **1b** (1.3 g, 30%); mp 138°C (dec.), R_f = 0.68. Found, %: C 38.51; H 3.47; I 29.18; N 9.45; S 7.44. $C_{14}H_{16}IN_3O_3S$. Calculated, %: C 38.77; H 3.69; I 29.31; N 9.69; S 3.79.

2-[(4-Methylphenyl)sulfonylcarbamido]-1-(4-nitrobenzyl)pyrimidinium Bromide (2a). 4-Nitrobenzyl bromide (2.16 g, 10 mmol) was added to a solution of compound **2** (2.92 g, 10 mmol) in DMF (10 ml).. The mixture was heated at 90°C for 3 h, cooled and ethyl acetate (150 ml) was added. The mass which separated solidified after intense stirring. Compound **2a** was isolated as a crystalline powder (2.3 g, 45%) after crystallization from a 1 : 1 mixture of ethanol and 2-propanol; mp 24-243°C, R_f = 0.51. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.68-9.37 (1H, br. s, NH); 8.98 (1H, dd, *J* = 2.1, *J* = 4.2, ArH); 8.77 (1H, dd, *J* = 2.1, *J* = 6.6, ArH); 8.28 (2H, dd, *J* = 4.2, *J* = 8.8, ArH); 7.60 (2H, d, *J* = 8.8, ArH); 7.24 (1H, dd, *J* = 4.2, *J* = 6.6, ArH); 5.68 (2H, s, CH_2); 3.40 (3H, s, CH_3). Found, %: C 44.58; H 3.29; Br 15.69; N 13.47; S 6.07. $C_{19}H_{18}BrN_5O_5S$. Calculated, %: C 44.86; H 3.54; Br 15.74; N 13.77; S 6.29.

1-methyl-2-[(4-Methylphenyl)sulfonylcarbamido]pyrimidinium Iodide (2b). Methyl iodide (1.42 g, 10 mmol) was added to a solution of compound **2** (2.92 g, 10 mmol) in 2-butanone (10 ml). After heating at 70°C for 2h, cooling and adding ethyl acetate (20 ml), compound **2b** crystallized after several hours. The crystals were

filtered off and washed with ethyl acetate to give **2b** (1.5 g, 34%); mp 183°C, R_f = 0.72. Found, %: C 33.67; H 3.21; N 12.63; I 29.01; S 7.19. $C_{13}H_{15}IN_4O_3S$. Calculated, %: C 33.93; H 3.45; N 12.90; I 29.25; S 7.37.

REFERENCES

1. M. Meyer, F. Chudziak, Ch. Shwanstecher, M. Schwanstecher, and U. Panten, *Brit. J. Pharmacol.,* **128,** 27 (1999).
2. V. Gendvilienė, D. Zablockaitė, H. Gurskaitė, I. Martšienė, and A. Stankevičius, *Lithuanian J. Cardiol.,***11**, 83 (2004).
3. N. J. Chambers and G. A. R. Johnston, US Pat. 5929082 (1999); http://v3.espacenet.com/textdoc?DB=EPODOC&IDX=US5929089&F=0