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SYNTHESIS OF BIOLOGICALLY ACTIVE AMMONIUM SALTS CONTAINING 4-(1*H*-PYRAZOL-1-YL)BUT-2-YNYL GROUP

K.S. BARSEGHYAN

Scientific and Technological Center of Organic and Pharmaceutical Chemistry
of National Academy of Sciences of RA
Azatutyan ave. 26, Yerevan, 0014, Republic of Armenia,
E-mail: ask-karine@mail.ru

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New ammonium salts containing 4-(1*H*-pyrazole-1-yl)but-2-ynyl group have been synthesized. The synthesized salts were established to have expressed antimicrobial activity against gram-positive and gram-negative microorganisms.

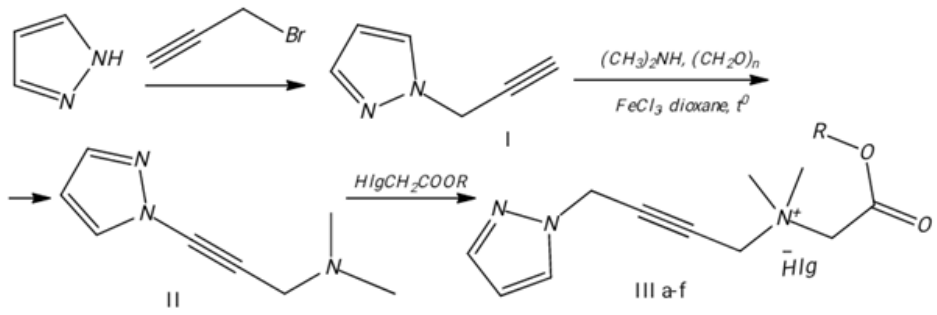
Scheme 1, table 1, ref. 10.

Quaternary ammonium salts (QAC), containing unsaturated groups, possess expressed biological activity. Particularly, QAC with propargyl type groups assure a wide spectrum of antimicrobial activity against gram-positive and gram-negative microorganisms, which are the main cause of many diseases, as well as microbial pollution of the environment [1-4]. According to literature data, substituted pyrazoles also reveal bactericidal properties [5, 6].

In order to obtain new biologically active ammonium compounds, it was interesting to combine the propargyl group with a pyrazole ring. Firstly, for this purpose, N,N-dimethyl-4-(1*H*-pyrazol-1-yl)but-2-yn-1-amine (II) was synthesized, based on propargylpyrazole (I) under the conditions of the Mannich reaction.

The initial ammonium salts **IIIa-f** were synthesized by interaction of synthesized amine **II** with alkyl esters of bromo(chloro)acetic acid in a molar ratio 1:1, in absolute diethyl ether.

Scheme 1.



R = CH_3 (a); C_8H_{17} (b); C_9H_{19} (c); $C_{10}H_{21}$ (d); $C_{11}H_{23}$ (e); $C_{12}H_{25}$ (f)

The synthesized ammonium salts **IIIa-f** are hygroscopic waxy substances (except compound **IIIa**), the purity of which were checked by TLC and the structures confirmed by the data of IR and ^{1}H NMR spectra.

The antimicrobial activity of compounds **IIIa-f** was studied by the method of "agar diffusion" and "serial dilutions" on meat-peptone broth (pH=7.2-7.4) when the bacterial load was 20 mln of microbial bodies per 1 ml of media [7, 8]. Gram-positive staphylococci (St. aureus 209p, 1) and gram-negative bacilli (St. dysenteriae Flexneri 6858, E. Coli 0-55) were used in experiments.

As a control under similar conditions was used the solution of the drug Furazolidone [9].

Study of the antimicrobial activity of compounds **IIIa-f** by the method of "agar diffusion", given in the table, showed that compound **IIIa** did not reveal antimicrobial activity.

Compounds **IIIb-d** had bactericidal effect against gram-positive and gram-negative test cultures inhibiting growth of microorganisms in the zone of 25-31 mm in diameter, which in some cases exceeded the control drug furazolidone. With the lengthening of the alkyl radical, the antimicrobial activity decreased.

Investigation of antimicrobial activity of compounds by the method of "two-fold serial dilutions" showed, that compounds with octyloxy- and nonyloxycarbonylmethyl groups were equal in activity to the control drug, inhibiting the growth of microorganisms at a concentration of 31.2 μg/ml. The activity of other compounds decreased with the extension of the alkyl radical.

Table 1

Antimicrobial activity of compounds III a-f

Compound	R	Diameter of the zone of growth inhibition (mm)				MIC, mkg/ml	
		St.aureus		Sh. dysenterae Flexneri 6858	E. Coli 0-55	St. aureus 209p	Sh. Dysenterae Flexneri 6858
		209p	1				
IIIa	CH_3	0	0	0	0	-	-
IIIb	C_8H_{17}	30	28	31	26	31.2	31.2
IIIc	C_9H_{19}	30	29	27	25	31.2	31.2
IIId	$C_{10}H_{21}$	29	27	26	20	62.5	125
IIIe	$C_{11}H_{23}$	30	27	26	20	62.5	125
IIIf	$C_{12}H_{25}$	31	23	25	20	250	250
Furazolidone		25±0	25.0±0	24.0±1.0	24.3±0.6	31.2	31.2

Compared with the previously synthesized quaternary ammonium salts with 4-diethylmino-, piperidino-, and morpholinobutin-2-yl groups [4], it can be seen that the introduction of the pyrazole ring into the QAS structure does not strongly affect the antimicrobial activity.

Hereby, the obtained results reveal the relationship between the chemical structure and biological activity, indicating the feasibility of searching for new effective compounds in this series.

Experimental

IR spectra were recorded on a Specord IR-75 instrument in mineral oil or thin layer. NMR spectra were registered on a Varian Mercury-300 (300 MHz) spectrometer from DMSO-d_6–CCl_4 solutions at 303 K; chemical shifts were reported relative to internal TMS. TLC analysis was performed using Silufol UV-254 plates eluting with butan-1-ol–ethanol–water–acetic acid, 10:7:6:4 (for ammonium salts) and detecting with iodine vapor.

The initial **1-(prop-2-yn-1-yl)-1*H*-pyrazole I** was synthesized by interaction of pyrazole with propargyl bromide in phase transfer catalysis conditions according to [10]. Yield 68%, bp 67-70 °C (15 mmHg), n_D^{20} 1.5040. IR spectrum, ν, cm^{-1}: 1550, 2140, 3109, 3500-3300 cm^{-1} region are caused by valence vibrations of C≡CH. Found, %: C 67.98, H 5.71, N 26.31. $C_6H_6N_2$ Calculated, %: C 67.92, H 5.66, N 26.42.

N,N-Dimethyl-4-(1*H*-pyrazol-1-yl)but-2-yn-1-amine II was synthesized under the conditions of the Mannich reaction. Yield 45%, bp 108-109 °C (2 mmHg), n_D^{20} 1.5010. IR spectrum, ν, cm^{-1}: 1530, 2190, 3107. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.28 s (6H, NCH_3), 3.29 t (2H,$(CH_3)_2NC\underline{H}_2$, *J* 2.1), 4.97 t (2H, NCH_2, *J* 2.1), 6.24 dd (1H, H-4 pyrazole, J^1 2.4, J^2 1.8), 7.45 dd (1H, H-3 pyrazole, J^1 1.8, J^2 0.7), 7.58 dd (1H, H-5 pyrazole, J^1 2.4,

J^2 0.7). Found, %: C 66.21, H 7.55, N 26.24. $C_9H_{13}N_3$. Calculated, %: C 66.26, H 7.97, N 25.77.

Ammonium salts III a-f. To a solution of 0.01 mole of amine **II** in 10 ml of anhydrous ether was added dropwise 0.01 mole of alkyl esters of bromo(chloro)acetic acid. The reaction mixture was kept at room temperature for 3-5 days. The formed salt was washed several times with anhydrous ether and dried in a desiccator over $CaCl_2$. Obtained salts are hygroscopic waxy substances, except salt **IIIa**. IR spectra, ν, cm^{-1}: 1135, 1180, 1730 (COO), 2230-2245 (C≡C), 1520-1530, 3100-3109 (pyrazole).

N-(2-methoxy-2-oxoethyl)-N,N-dimethyl-4-(1-*H*-pyrazol-1-yl)but-2-yn-1 ammonium bromide (IIIa). Yield 78%, mp. 99-100 °C, R_f 0.42. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.45 s (6H, N^+CH_3), 3.83 s (3H, OCH_3), 4.80 s (2H, CH_2COO), 4.81 t (2H, NCH_2, *J* 1.9), 5.20 t (2H, N^+CH_2, *J* 1.9), 6.23 dd (1H, 4-$H_{pyrazole}$, J^1 2.4, J^2 1.8), 7.40 dd (1H, 3-$H_{pyrazole}$, J^1 1.8, J^2 0.8), 7.80 dd (1H, 5-$H_{pyrazole}$, J^1 2.4, J^2 0.8). Found, %: N 13.36; Br^- 25.39. $C_{12}H_{18}BrN_3O_2$. Calculated, %: N 13.29; Br^- 25.32.

N,N-Dimethyl-N-(2-(octyloxy)-2-oxoethyl)-4-(1-*H*-pyrazol-1-yl)but-2-yn-1 ammonium chloride (IIIb). Yield 57%, R_f 0.39. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.90 t (3H, *J* 6.7, $CH_2C\underline{H}_3$); 1.24-1.40 m (10H, $(C\underline{H}_2)_5CH_3$); 1.63-1.73 m (2H, $OCH_2C\underline{H}_2$); 3.47 s (6H, NCH_3); 4.19 t (2H, *J* 6.8, OCH_2); 4.92 s (2H, CH_2COO); 4.94 t (2H, J 1.8, $C\underline{H}_2Pyr$), 5.20 t (2H, N^+CH_2, *J* 1.8), 6.20 dd (1H, 4-$H_{pyrazole}$, J^1 2.4, J^2 1.8), 7.38 dd (1H, 3-$H_{pyrazole}$, J^1 1.8, J^2 0.6), 7.80 dd (1H, 5-$H_{pyrazole}$, J^1 2.4, J^2 0.6). Found, %: N 11.29; Cl^- 10.01. $C_{19}H_{32}ClN_3O_2$. Calculated, %: N 11.37; Cl^- 9.61.

N,N-Dimethyl-N-(2-(nonyloxy)-2-oxoethyl)-4-(1-*H*-pyrazol-1-yl)but-2-yn-1 ammonium chloride (IIIc). Yield 68%, R_f 0.43. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.89 t (3H, J 6.8, $CH_2C\underline{H}_3$), 1.24-1.37 m (12H, $(C\underline{H}_2)_6CH_3$), 1.62-1.71 m (2H, $OCH_2C\underline{H}_2$), 3.49 s (6H, NCH_3), 4.19 t (2H, J 6.9, OCH_2), 4.93 s (2H, $C\underline{H}_2COO$), 4.96 t (2H, J 1.8, $C\underline{H}_2Pyr$), 5.20 t (2H, N^+CH_2, *J* 1.8), 6.21 dd (1H, 4-$H_{pyrazole}$, J^1 2.4, J^2 1.8), 7.38 dd (1H, 3-$H_{pyrazole}$, J^1 1.8, J^2 0.6), 7.81 dd (1H, 5-$H_{pyrazole}$, J^1 2.4, J^2 0.6). Found, %: N 11.21; Cl^- 9.35. $C_{20}H_{34}ClN_3O_2$. Calculated, %: N 10.95; Cl^- 9.26.

N,N-Dimethyl-N-(2-(decyloxy)-2-oxoethyl)-4-(1-*H*-pyrazole-1-yl)but-2-yn-1 ammonium chloride (IIId). Yield 65%, R_f 0.41. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.89 t (3H, J 6.6, $CH_2C\underline{H}_3$), 1.23-1.38 m (14H, $(C\underline{H}_2)_7CH_3$), 1.61-1.72 m (2H, $OCH_2C\underline{H}_2$), 3.48 s (6H, NCH_3), 4.19 t (2H, J 6.9, OCH_2), 4.92 s (2H, $C\underline{H}_2COO$), 4.95 t (2H, J 1.8, $C\underline{H}_2Pyr$), 5.20 t (2H, N^+CH_2, *J* 1.8), 6.21 dd (1H, 4-$H_{pyrazole}$, $J^1$2.2, J^2 1.8), 7.38 dd (1H, 3-$H_{pyrazole}$, J^1 1.8, J^2 0.6), 7.80 dd (1H, 5-$H_{pyrazole}$, $J^1$2.4, J^2 0.6). Found, %: N 10.48; Cl^- 9.03. $C_{21}H_{36}ClN_3O_2$. Calculated, %: N 10.57; Cl^- 8.93.

N,N-Dimethyl-N-(2-(undecyloxy)-2-oxoethyl)-4-(1-*H*-pyrazole-1-yl)but-2-yn-1 ammonium chloride (IIIe). Yield 61%, R_f 0.44. ^{1}H NMR

spectrum, δ, ppm (*J*, Hz): 0.89 t (3H, J 6.6, $CH_2C\underline{H}_3$), 1.22-1.36 m (16H, $(C\underline{H}_2)_8CH_3$), 1.60-1.72 m (2H, $OCH_2C\underline{H}_2$), 3.49 s (6H, NCH_3), 4.18 t (2H, J 6.9, OCH_2), 4.92 s (2H, $C\underline{H}_2COO$), 4.95 t (2H, J 1.8, $C\underline{H}_2\underline{Pyr}$), 5.20 t (2H, N^+CH_2, *J* 1.8), 6.20 dd (1H, 4-$H_{pyrazole}$, $J^1$2.4, J^2 1.8), 7.38 dd (1H, 3-$H_{pyrazole}$, $J^1$1.8, J^2 0.6), 7.81 dd (1H, 5-$H_{pyrazole}$, $J^1$2.4, J^2 0.6). Found, %: N 10.34; Cl^- 8.78. $C_{22}H_{38}ClN_3O_2$. Calculated, %: N 10.21; Cl^- 8.63.

N,N-Dimethyl-N-(2-(dodecyloxy)-2-oxoethyl)-4-(1-*H*-pyrazole-1-yl)but-2-yn-1 ammonium chloride (IIIf). Yield 75%, R_f 0.40. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.89 t (3H, J 6.7, $CH_2C\underline{H}_3$), 1.22-1.37 m (18H, $(C\underline{H}_2)_9CH_3$), 1.62-1.71 m (2H, $OCH_2C\underline{H}_2$), 3.48 s (6H, NCH_3), 4.18 t (2H, J 6.9, OCH_2), 4.92 s (2H, $C\underline{H}_2COO$), 4.95 t (2H, J 1.8, $C\underline{H}_2\underline{Pyr}$), 5.20 t (2H, N^+CH_2, *J* 1.8), 6.21 dd (1H, 4-$H_{pyrazole}$, $J^1$2.3, J^2 1.8), 7.38 dd (1H, 3-$H_{pyrazole}$, $J^1$1.8, J^2 0.6), 7.80 dd (1H, 5-$H_{pyrazole}$, $J^1$2.3, J^2 0.6). Found, %: N 11.48; Cl^- 9.53. $C_{23}H_{40}ClN_3O_2$. Calculated, %: N 11.37; Cl^- 9.61.

4-(1Հ-ՊԻՐԱԶՈԼ-1-ԻԼ)ԲՈՒԹ-2-ԻՆԻԼ ԽՈՒՄԲ ՊԱՐՈՒՆԱԿՈՂ ԿԵՆՍԱԲԱՆՈՐԵՆ ԱԿՏԻՎ ԱՄՈՆԻՈՒՄԱՅԻՆ ԱՂԵՐԻ ՍԻՆԹԵԶ

ԲԱՐՍԵՂՅԱՆ Կ. Ս.

Ամոնիումային աղերի հակաբակտերիալ հատկությունների ուսումնասիրության նպատակով սինթեզվել են 4-(1Հ-պիրազոլ-1-իլ)բութ-2-ինիլ խումբ պարունակող ամոնիումային աղեր, որոնցում համատեղվում են պիրազոլի օղակի ֆարմակոֆոր բաղադրիչները, պրոպարգիլային խումբը և ամոնիումային կատիոնը: Պրոպարգիլպիրազոլի հիման վրա սինթեզված N,N-դիմեթիլ-4-(1*H*-պիրազոլ-1-իլ)բութ-2-ին-1-ամինի և մոնոքլոր/բրոմ/քացախաթթվի ալկիլ էսթերների փոխազդեցության արդյունքում ստացվել են մի շարք ամոնիումային աղեր: Ցույց է տրվել, որ սինթեզված աղերի մի մասը ցուցաբերում է արտահայտված հակաբակտերիալ ակտիվություն գրամբացասական և գրամդրական միկրոօրգանիզմների հանդեպ:

СИНТЕЗ БИОЛОГИЧЕСКИ АКТИВНЫХ АММОНИЕВЫХ СОЛЕЙ, СОДЕРЖАЩИХ 4-(1*H*-ПИРАЗОЛ-1-ИЛ)БУТ-2-ИНИЛЬНУЮ ГРУППУ

БАРСЕГЯН К. С.

Научно-технологический центр органической и фармацевтической химии
Национальной академии наук Республики Армения
Армения,0014, Ереван, пр. Азатутян, 26
E-mail: ask-karine@mail.ru

С целью исследования антибактериальных свойств синтезированы аммониевые соли, содержащие 4-(1*H*-пиразол-1-ил)бут-2-инильную группу, в которых сочетаются фармакофорные фрагменты пиразола, пропаргильная группа и четвертичная аммониевая соль. На синтезированной основе пропаргилпиразола N,N-диметил-4-(1*H*-пиразол-1-ил)бут-2-ин-1-амина и алкиловых эфиров моно-

хлор(бром)уксусной кислоты получен ряд аммониевых солей. Показано, что некоторые из них проявляют выраженную антибактериальную активность в отношении грамположительных и грамотрицательных микроорганизмов.

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