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Synthesis and Biological Study of Dialkyl(4-hydroxybut-2-ynyl)(3-phenyl-2,3-dichloroallyl)ammonium Chlorides, Their Intramolecular Cyclization and Recyclization of Obtained Products

A. R. GEVORGYAN

Institute of Organic Chemistry, Scientific and Technological Center of Organic and Pharmaceutical Chemistry, National Academy of Sciences of Armenia, Yerevan, Armenia

National Polytechnic University of Armenia, Yerevan, Armenia

E-mail: hasmikgevorgyan973@gmail.com

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Abstract

Potentially bioactive dialkyl(4-hydroxybut-2-ynyl)(3-phenyl-2,3-dichloroallyl)ammonium chlorides were synthesized. By base-catalyzed intramolecular cyclization of these salts and subsequent intramolecular recyclization of cyclic products 4-dialkylaminomethyl-5-chloro-1,3-dihydronaphto[1,2-c]furans were obtained. According to biological studies, dimethyl(4-hydroxybut-2-ynyl)(3-phenyl-2,3-dichloroallyl)ammonium chloride has anticoagulant and strongly pronounced antioxidant properties.

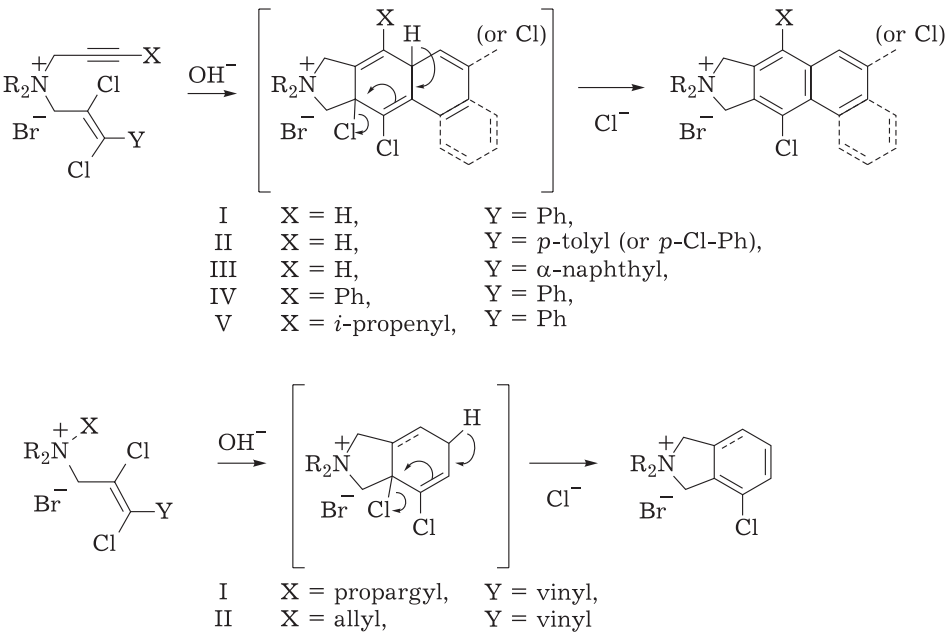
Key words: intramolecular cyclization-dehydrochlorination, dialkyl(4-hydroxybut-2-ynyl)(3-phenyl-2,3-dichloroallyl)ammonium chlorides, intramolecular recyclization, dihydronaphto[1,2-c]furan derivatives, biological activity, antioxidant, anticoagulan

INTRODUCTION

It is known that the key role in the molecular mechanisms of pathogenesis of many diseases is played by disbalance in the system of free radical oxidation and antioxidant protection. In this connection, the synthesis of new antioxidant compounds and the studies of their antioxidant properties are an urgent problem [1].

Some representatives of the salts containing β, γ-unsaturated group along with various enyne fragments, and the derivatives of isoindolynium salts obtained on the basis of base-catalyzed intramolecular cyclization exhibit high pharmacological activity. The compounds under consideration possess essential pharmacological properties, such as hypo- and hypertension activity, nonnarcotic analgesic action, anticoagulant, antioxidant properties *etc*. The pharmacological activity of these compounds is protected by numerous Authors' Certificates of the USSR and two patents of the Republic of Armenia [2–4].

It was demonstrated previously that the interaction of the aqueous solutions of salts containing β, γ-unsaturated groups, along with various 3-aryl-2,3-dichloroallyl or 2,3-dichloro-2,4-pentadienyl groups, with aqueous alkali results in the formation of the derivatives of 4-chlorobenzo[*f*] isoindolynium, -isoindolinium and –dihydroisoindolinium, respectively, with a high yield (Scheme 1)



Scheme 1.

[5–9]. The latter compounds could be formed *via* two routes (*A* and *B*). Along route *A*, the initial salt undergoes cyclization at first, then dehydrochlorination of the intermediate cyclic product occurs, while along route *B* dehydrochlorination precedes cyclization. The authors of [6, 7] clearly established that cyclization of the salts under tests precedes dehydrochlorination.

The goal of the present work was to develop a procedure for the synthesis of new biologically active derivatives of isoindolynium on the basis of expansion and development of the area of application of base-catalyzed intramolecular cyclization of ammonium salts containing 4-hydroxybut-2-inyl group along with various enyne fragments

EXPERIMENTAL

Procedures for the synthesis and characterization of the compounds under investigation

Initial dimethyl-, diethyl(3-phenyl-2,3-dichloroallyl)amines were obtained according to the procedure described in [5].

Synthesis of initial salts 1a, b (general procedure). Dimethyl- (**1a**), diethyl(4-hydroxybut-2-ynyl)(3-phenyl-2,3-dichloroallyl)ammonium chlorides (**1b**) were obtained with high yields by alkylation of 31 mmol of the corresponding amine by 4.86 g (46 mmol) of 4-hydroxy-1-chloro-but-2-yne [10] (the molar ratio amine/alkylating agent = 1 : 1.5) in 6 ml of acetonitrile. Self-heating was not observed. The reaction mixture was heated for 3–4 h, then the solvent was evaporated until dry under reduced pressure. The residue was washed with absolute diethyl ether (3 × 30 ml), the salts were dissolved in absolute ethanol, and then the salts were isolated with the help of absolute ether: salt **1a** was obtained in the crystal state, and salt **1b** in a honey-like form.

Dimethyl(4-hydroxybut-2-ynyl) (3-phenyl-2,3-dichloroallyl)ammonium chloride (1a). Yield: 7.4 g (71 %), T_m 136–138 °C (abs. ethanol). IR spectrum, ν, cm^{-1}: 710, 770 (monosubstituted benzene ring), 1520, 1600, 3050 (aromatic ring), 1670 (tetrasubstituted double bond), 2225 (disubstituted acetylene bond), 3100–3350 (OH group). NMR 1H spectrum δ, ppm (*J*, Hz): 3.47 (6H, s, CH_3); 4.21 (2H, dt, *J* = 5.4, 2.0, OCH_2); 4.91 (2H, t, *J* = 2.0, $NCH_2C{\equiv}C$); 4.94 (2H, s, $N\underline{CH_2}CCl{=}CCl$); 5.53 (1H, t, *J* = 5.4, OH); 7.40–7.48 (3H, m, C_6H_5), 7.58–7.62 (2H, m, C_6H_5). NMR ^{13}C spectrum δ, ppm: 48.8 (CH_2); 50.1 ($2CH_3$); 55.3 (CH_2); 65.1 (CH_2); 72.1 (≡C); 92.6 (≡C); 118.5 (C); 127.9 (2CH); 128.4 (2CH); 129.5 (CH); 135.6 (C); 139.4 (C). Found, %: C 54.04; H 5.29; Cl 31.55; N 4.33 $C_{15}H_{18}C_{l3}NO$. Calculated, %: C 53.83; H 5.42; Cl 31.78; N 4.19.

Diethyl(4-hydroxybut-2-ynyl)(3-phenyl-2,3-dichloroallyl)ammonium chloride (1b). Yield 8.7 g (78 %). IR spectrum, ν, cm^{-1}: 700, 760 (monosubstituted benzene ring), 1560, 1600, 3050 (aromatic ring), 1675 (tetrasubstituted double bond), 2220 (disubstituted acetylene bond), 3100–3340 (OH group). NMR ^1H spectrum δ, ppm. (*J*, Hz): 1.42

(6H, t, J = 7.2, C<u>H</u>$_3$); 3.68 (4H, q, J = 7.2, CH_2CH_3); 4.21 (2H, dt, J = 4.8, 1.8, OCH_2); 4.91 (2H, t, J = 1.8, NC<u>H</u>$_2$C≡C); 4.94 (2H, s, NC<u>H</u>$_2$CCl=CCl); 5.61 (1H, t, J = 4.8, OH); 7.41– 7.48 (3H, m, C_6H_5), 7.58–7.62 (2H, m, C_6H_5). Found, %: C 56.54; H 6.22; Cl 29.02; N 3.71. $C_{17}H_{22}Cl_3NO$. Calculated, %: C, 56.29; H, 6.11; Cl, 29.32; N, 3.86.

Intramolecular cyclization of salts 1a, b and subsequent intramolecular recyclization of cyclic products (a general procedure). 10.5 mL of 3 M KOH solution was added to the solution of 21 mmol of salt **1a**, **b** in 5.5 mL of water (the ratio of salt/alkali = 1 : 1.5). The temperature of the reaction mixture was increased by self-heating from 25–28 to 43–45 °C. The reaction mixture was extracted with a solution of ether / hexane at a volume ratio of 1 : 1 (2 × 30 mL). Titration of the extract by the solution of 0.05 M H_2SO_4 revealed the presence of amine (10–12 %). The extract was acidified with hydrochloric acid to achieve the acidic medium. Amines were isolated through alkalization followed by extraction with a mixture of ether/hexane at a volume ratio of 1 : 1 (2 × 30 mL). The extract was washed with water and dried with the help of $MgSO_4$. After solvent evaporation, recyclization amines **3a, b** were isolated. Then a double molar amount of KOH was added to the mixture, and the mixture was heated to 75–80 °C and kept for 2 h. The reaction mixture was extracted with the solution of ether/hexane at the volume ratio of 1 : 1 (2 × 30 mL). Recyclization amines **3a, b** were obtained by the usual treatment of the extract. In both cases, a black resinous substance was obtained from the reaction mixture. We failed to identify it.

4-Dimethylaminomethyl-5-chloro-1,3-dihydronaphtho[1,2-*c*]furan (3a). Yield 3.5 g (56 %), T_b 145–146 °C (1 mm Hg), T_m of pycrate 146 °C (absolute ethanol), T_m of chlorohydrate 208–210 °C (absolute ethanol). IR spectrum, ν, cm^{-1}: 730, 770 (1,2-substituted benzene ring); 1040, 1080, (–CH_2–O–CH_2– group), 1600, 3030, 3050 (aromatic ring). NMR ^{1}H spectrum, δ, ppm (J, Hz): 2.24 (6H, s, CH_3); 3.72 (2H, s, NCH_2); 5.27 (2H, t, J = 3.0, OCH_2); 5.38 (2H, t, J = 3.0, OCH_2); 7.53–7.62 (3H, m, Ph), 8.28–8.32 (1H, m, Ph). NMR ^{13}C spectrum δ, ppm: 44.8 (2C, CH_3); 58.5 (NCH_2); 72.2 (OCH_2); 73.7 (OCH_2); 123.7 (CH); 125.1 (CH); 126.1 (CH); 126.3 (CH); 126.9 (CH); 128.8 (CH); 129.8; 133.4; 136.1, 137.2 (Ph). Found, %: C 68.49; H 6.23; Cl 13.77; N 5.19. $C_{15}H_{16}ClNO$. Calculated, %: C 68.83; H 6.12; Cl 13.57; N 5.35.

4-Diethylaminomethyl-5-chloro-1,3-dihydronaphtho[1,2-*c*]furan (3b). Yield 3.4 g (76 %), T_m 55–57 °C, T_m of pycrate 175–177 °C (absolute ethanol), T_m of chlorohydrate 155–157 °C (absolute ethanol). IR spectrum, ν, cm^1: 740, 770 (1,2-substituted benzene ring); 1040, 1080, (–CH_2–O–CH_2– group), 1600, 3010, 3050 (aromatic ring). NMR ^{1}H spectrum δ, ppm (J, Hz): 1.04 (6H, t, J = 7.2, CH_3); 2.52 (4H, q, J = 7.2, N(<u>CH</u>$_2$$CH_3$)$_2$); 3.88 (2H, s, NCH_2); 5.29 (2H, t, J = 3.0, OCH_2); 5.37 (2H, t, J = 3.0, OCH_2); 7.50–7.62 (3H, m, Ph), 8.23– 8.32 (1H, m, Ph). NMR ^{13}C spectrum δ, ppm: 11.2 (2C, CH_3); 46.0 (2C, NCH_2); 53.0 (NCH_2); 72.0 (OCH_2); 73.9 (OCH_2); 123.7 (CH); 124.9 (CH); 126.1 (CH); 126.2 (CH); 126.8 (CH); 129.5 (CH); 129.6; 129.7; 133.4; 137.1 (Ph). NMR ^{1}H spectrum of chlorohydrate of **3b**, δ, ppm (J, Hz): 1.45 (6H, t, J = 6.7, CH_3); 3.15-3.32 (4H, m, N<u>CH</u>$_2$$CH_3$); 4.51 (2H, d, J = 5.6, NCH_2); 5.47 (2H, broadened s., OCH_2); 5.68 (2H, broadened s., OCH_2); 7.62–7.75 (3H, m, Ph), 8.31–8.38 (1H, m, Ph), 11.59 (1H, broadened s, NH_4^+). Found, %: C 67.36; H 6.85; Cl 12.43; N 5.09. $C_{17}H_{20}ClNO$. Calculated, %: C 70.46; H 6.96; Cl 12.23; N 4.83.

Physicochemical methods of investigation

IR spectra of salts **1a**, **b** (films from chloroform) and amines **3a**, **b** (thin layer) were recorded with a Specord IR-75 spectrometer.

NMR ^{1}H and ^{13}C spectra were recorded with a Varian Mercury-300 VX spectrometer (300.077 and 75.463 MHz, respectively) in DMSO-d_6-CCl_4. Chemical shifts are given with respect to the signal of TMS as an internal standard.

Elemental analysis was carried out with the help of a compact element analyzer Vario MICRO cube.

The melting temperatures of salts were determined using an instrument manufactured by VEB Wage-Technik Rapido Radebeul Betriebdes VEB Kombinat NAGEMA DDR.

Blood analysis was carried out with the help of a hemocoagulator Stago STart-4 (France).

Procedure for biological studies

Experiments were carried out with outbred white male rats 180–200 g in mass kept with a usual food allowance. A solution of 0.6 mg of salt **1a** in 1 mL of water was introduced to the experimental animals, while reference animals received 1 mL of water. The animals were decapitated under soft ether anesthesia, the isolated liver was washed with the physiological solution, cleared from blood vessels, and homogenized in a *tris*-HCl buffer (pH 7.4). The level of lipid peroxides was determined in a non-enzymatic system of re-oxidation relying on the yield of the final

product – malonic dialdehyde (MDA) which interacts with thiobarbituric acid to form a complex compound in the form of a pink-coloured chromogen; the intensity of its colouring was recorded with a spectrophotometer at the wavelength of λ = 535 nm) and corresponded to the amount of the formed perioxide.

RESULTS AND DISCUSSION

As a continuation of the investigations, we studied the behaviour of dimethyl- (**1a**), diethyl(4-hydroxybut-2-ynyl)(3-phenyl-2,3-dichloroallyl)ammonium (**1b**) chlorides with respect to the aqueous alkali.

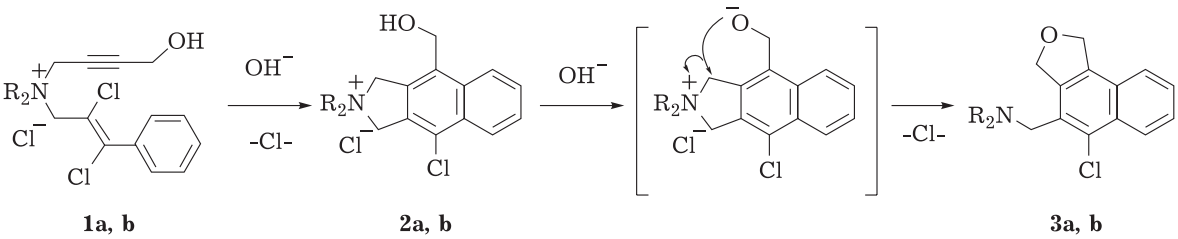
One can see in the structure of the salts under tests that theoretically there are several possible directions for the chemical transformations of these compounds in the alkaline aqueous medium (Scheme 2). On the basis of the results of previous studies in this area [5–9], it was assumed that the cyclization of salts **1a**, **b** also precedes dehydrochlorination leading to the formation of potentially bioactive chlorides of 2,2-dimethyl- (**2a**) and 2,2-diethyl-4-hydroxymethyl-9-chlorobenzo[*f*]isoindolinium (**2b**).

Under the conditions of water-alkaline cleavage, similarly to the halides of 4-hydroxy-methylisoindolinium and their condensed derivatives [11], salt **2a**, **b** also may undergo intramolecular recyclization with the formation of 4-dimethyl- (**3a**) and 4-diethylaminomethyl-5-chloro-1,3-dihydronaphtho[1,2-c]furans (**3b**).

In the interaction of salts **1a**, **b** with the 3 M KOH solution in the molar ratio salt/alkali = 1 : 1.5, the temperature of the reaction mixture rises slowly due to moderate self-heating from 25–28 to 43–45 °C. Under these conditions, the products of cyclization of salts **1a**, **b** undergo intramolecular re-cyclization forming **3a**, **b** in a yield of 10–12 %. All attempts to obtain the corresponding cyclic products **2a**, **b** in the crystalline form turned out to fail. As a consequence, cyclization of salts **1a**, **b** was carried out, followed by re-cyclization of cyclic salts **2a**, **b** under the action of a double molar amount of KOH per one mole of the initial salt under heating with a reflux condenser at 85–90 °C for 2 h. Re-cyclization amines **3a**, **b** are formed in a yield of 56 and 76 %, respectively; chlorohydrates of these salts do not give a depression of melting temperatures with chlorohydrates of the amines obtained through cyclization of salts **1a**, **b** under the conditions of base catalysis.

Cyclization of salts **1a**, **b** followed by re-cyclization of cyclic salts **2a**, **b** is also accompanied by resinification. In both cases, a resin-like black-coloured substance was isolated from the reaction mixture. Its identification failed.

The addition of aqueous alkali to the aqueous solution of salts **1a**, **b** at the ratio of salt/alkali = 1 : 1.5 causes self-heating of the reaction mixture, which is another evidence that cyclization pre-



1a, b **2a, b** **3a, b**

1a, 2a, 3a: R = CH_3,
1b, 2b, 3b: R = C_2H_5

Scheme 2.

TABLE 1

Effect of salt **1a** on the shifts of some parameters of the blood clotting system

Parameter	Reference	Experiment (salt **1a**)
Prothrombin time, s	16.4	18.6
Thrombin time, s	14.6	16.5
Activated partial thromboplastic time, s	30.0	33.5
Fibrinogen amount, mg	325	335

cedes dehydrochlorination because dehydrochlorination is an endothermic process.

To reveal the antioxidant properties of salt **1a**, its biological examination was carried out. It was shown that the differences in MDA content (nM/mg of protein) in the liver of experimental and reference animals are 63 % (reference 10.58±0.22, experiment (salt **1a**) 6.66±0.26). Thus, salt **1a** exhibits strongly pronounced antioxidant activity. In addition, the effect of salt **1a** on the shifts of some parameters of the blood clotting system was studied (Table 1). It follows from the analysis of these data that salt **1a** possesses anticoagulant properties.

CONCLUSION

Potentially bioactive chlorides of dialkyl(4-hydroxybut-2-ynyl)(3-phenyl-2,3-dichloroallyl)ammonium salts were synthesized. Base-catalyzed intramolecular cyclization of these salts followed by intramolecular re-cyclization of the cyclic products leads to 4-dialkylaminomethyl-5-chloro-1,3-dihydronaphtho[1,2-c]furans. On the basis of biological studies, it was shown that dimethyl (4-hydroxybut-2-ynyl)(3-phenyl-2,3-dichloroallyl)ammonium chloride exhibits anticoagulant action with respect to the reference, as well as strongly pronounced antioxidant activity.

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