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THE BEHAVIOR OF *p*-BIS{3-[N-(3-CHLORO-BUTEN-2-YL)PYRROLIDINIO(PIPERIDINIO OR MORPHOLINIO)]PROPYN-1-YL}BENZENE DICHLORIDES IN AN AQUEOUS BASE MEDIUM

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In aqueous base medium p-bis{3-[N-(3-chlorobuten-2-yl)pyrrolidinio (piperidinio or morpholinio)]-propyn-1-yl}benzene dichlorides undergo a two-way dehydrochlorination-cyclization reaction to form benzo[5,6-a:5',6'-c]bis(2,2-tetramethylene- or -2,2-pentamethylene-4-methylisoindolinium) and benzo-[5,6-a:5',6'-c]bisspiro(4-methylisoindoline-2,4'-morpholinium) dichlorides.

Keywords: benzo[5,6-*a*:5',6'-*c*]bisspiro(4-methylisoindoline-2,4'-morpholinium), *p*-bis(3-morpholino-propyn-1-yl)benzene, benzo[5,6-*a*:5',6'-*c*]bis(2,2-pentamethylene-4-methylisoindolinium) dichlorides, *p*-bis-{3-[N-(3-chlorobuten-2-yl)pyrrolidinio(piperidinio or morpholinio)]propyn-1-yl}benzene dichlorides, two-way dehydrochlorination-cyclization reaction.

We have previously shown that the dehydrochlorination-cyclization of dialkyl(3-chlorobuten-2-yl)(3-α-naphthylpropargyl)ammonium salts leads to the formation of 2,2-dialkyl-4-methylnaphtho[*f*]isoindolinium chlorides [1].

With the aim or preparing a novel series of nitrogen heterocycles with a phenanthrene fragment we have studied the behavior of the *p*-bis{3-[N-(3-chlorobuten-2-yl)pyrrolidinio(piperidinio or morpholinio)]propyn-1-yl}benzene dichlorides (**1a), (1b), (1c)** respectively) with aqueous base.

The formation of the final product can be achieved by two routes differentiated by the sequence of the cyclization and dehydrochlorination stages. In route **A** the starting salts are first dehydrochlorinated and the *p*-bis{3-[N-(butyn-2-yl)pyrrolidinio(piperidinio, morpholinio)]propyn-1-yl}benzene dichlorides (**2a), (2b), (2c)** respectively obtained are cyclized to compounds **3a-c**. In route **B** the cyclization precedes the dehydrochlorination. With the object of studying the order of the reactions indicated above we have examined the reaction of the salts **1a-c** with a threefold molar excess of aqueous base at room temperature.

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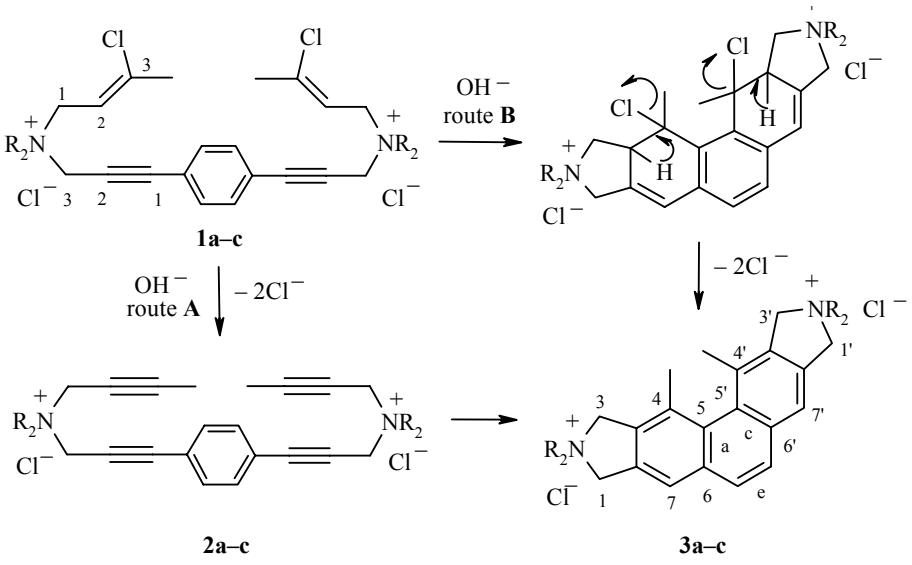
It was found that standing the reaction mixture of salts **1a-c** at 22-23ºC for 46-48 h gave 1.9, 1.86, and 1.83 mol respectively of ionic halogen from 1 mol of the starting salt. It should be noted that a mixture of compounds **3a-c** with the dehydrochlorination products **2a-c** not undergoing cyclization is formed under these conditions with an overall yield of 69-72%.



1a–c **2a–c** **3a–c**

1–3 a $R_2 = (CH_2)_4$, **b** $R_2 = (CH_2)_5$, **c** $R_2 = (CH_2)_2O(CH_2)_2$

According to TLC and IR spectroscopic data the salts **2a-c** predominate in the mixture. In the case of the mixture of salts **2b,c** and **3b,c** it was found that addition of 0.4 equivalents of aqueous base per 1 mol of the salt mixture, holding the reaction mixture at room temperature for 3 days, and then heating to 80-85ºC for 3-4 h caused complete cyclization of salts **2b,c**. The data obtained suggests that the dehydrochlorination of salts **1a-c** is analogous to dehydrochlorination of 3-arylpropargyl salts [1, 2] and precedes the cyclization.

It should also be noted that the cyclic salts **3b,c** are obtained in 62 and 64% yields respectively upon directly heating the starting salts **1b,c** at 80-85ºC for 6-7 h. All attempts to obtain the corresponding product by dehydrochlorination-cyclization of salt **1a** were unsuccessful. Together with the cyclic salts **3b,c** there were also obtained dark colored salts which were readily soluble in water and in alcohol but which we were unable to identify. It should be mentioned that, in contrast to other 3-arylpropargyl analogs [1, 2], both at room temperature and also when directly heated in aqueous base medium, only salt **1c** also undergoes nucleophilic splitting off to give *p*-bis(3-morpholinopropyn-1-yl)benzene in 12% yield. Vinylacetylene and chloroprene were revealed qualitatively.

The IR spectra of the mixture of salts **2a-c** and **3b,c** showed the absence of absorption for a disubstituted double bond at 1650, 1670 cm^{-1}. At the same time, the intensity of the disubstituted acetylenic bond absorption is increased when compared with the starting salts **1a-c**.

The IR spectra of the cyclic salts **3b,c** showed the absence of an absorption typical of a disubstituted double bond, triple bond, or *p*-substituted benzene ring at 1650-1680, 2230-2240, and 840 cm^{-1} respectively as seen in the salts **1b,c** and **2b,c**. Absorption bands for 1,2,3,4- tetrasubstituted and pentasubstituted benzene ring were found at 730-780, 800-830, and 870-890 cm^{-1} respectively typical for salts **3b,c** and aromatic absorption bands at 1580, 1600, 3040, and 3060 cm^{-1}.

The structure of the cyclic salts **3b,c** was also confirmed by ^{1}H and ^{13}C NMR spectroscopic methods. The spectra of the compounds reported above agree well with their proposed structures.

EXPERIMENTAL

IR spectra were taken on a UR-20 spectrometer for KBr tablets or in vaseline oil. TLC of salts **3b,c** was carried out on Silufol UV-254 plates in the system *n*-butanol–ethanol–water–acetic acid (8:2:3:1) and revealed using iodine vapor. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Mercury-300 spectrometer (300 and 75 MHz respectively) at 30ºC (303K) using DMSO-d_6 with TMS as internal standard. The composition of the compounds obtained was confirmed by elemental analysis.

Synthesis of the Starting Salts 1a-c (General Method). A 3 fold molar amount of 1,3-dichloro-2-butene was added at room temperature to a solution of the corresponding amines – *p*-bis(3-pyrrolidino-propyn-1-yl)benzene [4], *p*-bis(3-piperidinopropyl-1-yl)benzene [4], or *p*-bis(3-morpholinopropyn-1-yl)benzene [3] (10 mmol) in absolute benzene (10 ml) and acetonitrile (5 ml). After 3 days the corresponding salts **1a-c** were filtered off and washed with absolute benzene (2×10 ml).

***p*-Bis{[N-(3-chlorobuten-2-yl)pyrrolidinio]propyn-1-yl}benzene Dichloride (1a)**. Yield 97%; mp 109-110ºC (abs. EtOH). IR spectrum, ν, cm^{-1}: 840, 870, 1580, 1650, 2240, 3060. Found, %: Cl 26.58; N 5.35. $C_{28}H_{36}Cl_4N_2$. Calculated, %: Cl 26.20; N 5.17.

***p*-Bis{[N-(3-chlorobuten-2-yl)piperidinio]propyn-1-yl}benzene Dichloride (1b)**. Yield 97%; mp 220ºC (abs. EtOH). IR spectrum, ν, cm^{-1}: 840, 875, 1600, 1670, 2250, 3050. Found, %: Cl 25.26; N 5.17. $C_{30}H_{40}Cl_4N_2$. Calculated, %: Cl 24.91; N 4.91.

***p*-Bis{[N-(3-chlorobuten-2-yl)morpholinio]propyn-1-yl}benzene Dichloride (1c)**. Yield 97%; mp 165ºC (abs. EtOH). IR spectrum, ν, cm^{-1}: 825, 840, 1580, 1600, 1660, 2240, 3030, 3060. Found, %: Cl 25.10; N 5.13. $C_{28}H_{36}Cl_4N_2O_2$. Calculated, %: Cl 24.74; N 4.88.

Preparation of the Cyclic Salts 3a-c (General Method). A (at room temperature). A 3N solution of KOH (3.7 ml) was added to a solution of the corresponding salt **1a-c** (3.7 mmol) in water (3 ml) (molar ratio of salt to base 1:3). By titration it was shown that 1.9, 1.86, and 1.83 mol of ionic halogen per 1 mol of respective salt taken was formed after standing at room temperature for 72-74 h. The reaction mixture was then extracted with benzene (2×30 ml). Only in the case of salt **1c** did titration show the presence of amine (12%). The benzene extract was treated with aqueous HCl solution (15%) to acid reaction, the hydrochloric acid layer was basified with an aqueous NaOH solution (20%), and extracted with benzene to give the *p*-bis(3-morpholinopropyn-1-yl)benzene which did not depress the melting point of a known sample [3]. The reaction mixture after extraction with benzene was acidified with aqueous HCl solution (15%) and evaporated to dryness *in vacuo*. The residue was extracted with absolute ethanol and the mixture of salts **2a-c** and **3a-c** (~ 2.5-3.5 mmol, overall yield ~ 69-72%) was precipitated from the alcohol extract using absolute ether. A 3N solution of KOH (0.4 ml or 0.5 ml) was then added to a solution of the mixture of salts **2b, 3b** (3 mmol) and salts **2c, 3c** (3.5 mmol) in water (2-3 ml) (molar ratio of salt to base 2.5:1). The mixture obtained was heated for 4-5 h at 80-85ºC when the salts **2b,c** were fully cyclized to give the salts **3b,c**.

B (at 80-85ºC). KOH solution (3N, 3-4 ml) was added to a solution of salt **1a-c** (3-4 mmol) in water (3-4 ml) (molar ratio of salt to base 1:3). The reaction mixture was heated at 80-85ºC for 6-7 h. Titration showed the formation of 1.92, 1.85, and 1.88 mol respectively of ionic halogen per 1 mol of the salt taken. The reaction mixture was extracted with benzene (2×30 ml). Only in the case of salt **1c** did the extract show the presence of amine (12%). The usual treatment of the benzene extract (see method A) gave *p*-bis(3-morpholino-propyn-1-yl)benzene [3]. After standing for 2-3 h at room temperature the reaction mixture was filtered to separate the cyclic salt fractions **3b,c**. The mother liquor was treated with aqueous HCl solution (15%) to acid reaction and the solvent was evaporated to dryness *in vacuo*. The remaining fraction of salts **3b,c** were extracted from the residue using absolute ethanol. The salts were separated from the alcohol solution by filtration with cooling to -3 to -5ºC. Dark colored salts were also precipitated from the mother liquor using absolute ether but could not be identified.

It should be noted that, in the case of salt **1a**, the corresponding cyclic product **3a** could not be separated and identified by either of the two methods.

Benzo[5,6-*a*:5',6'-*c*]bis[2,2-pentamethylene-4-methylisoindolinium Dichloride (3b). Yield 62%, not melting, carbonizes above 250ºC. IR spectrum, ν, cm^{-1}: 730, 780, 870, 1600, 3050. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.67 (4H, br. q, *J* = 6.0, $N(CH_2)_2C\underline{H_2}$); 1.88-2.08 (8H, m, $NC\underline{H_2}CH_2$); 2.48 (6H, s, CH_3); 3.63 and 3.73 (4H, t, *J* = 5.6, NCH_2); 5.18 (4H, s, 1- and 1'-CH_2); 4.97 and 5.24 (2H, d, *J* = 14.9, 3- and 3'-CH_2); 7.74 (2H, s, Ar CH); 7.85 (2H, br. s, 7- and 7'-Ar–CH). ^{13}C NMR spectrum, δ, ppm: 19.90 (4- and 4'-CH_3); 20.56 ($N(CH_2)_2\underline{C}H_2$); 20.80 ($NCH_2\underline{C}H_2$); 60.60 ($NCH_2$); 66.34 (3- and 3'-$CH_2$); 66.93 (1- and 1'-$CH_2$); 119.51, 126.89, 129.39, 131.09, 131.48, 132.03 and 134.13 (Ar–C). Found, %: Cl 14.59; N 5.43. $C_{30}H_{38}Cl_2N_2$. Calculated, %: Cl 14.29; N 5.63.

Benzo[5,6-a:5',6'-*c*]bisspiro[4-methylisoindoline-2,4'-morpholinium] Dichloride (3c). Yield 61%, not melting, carbonizes above 250ºC. IR spectrum, ν, cm^{-1}: 730, 770, 810, 870, 1570, 1600, 3040, 3060. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.49 (6H, s, CH_3); 3.74 and 3.83 (4H, t, *J* = 4.8, OCH_2); 3.99-4.18 (8H, m, NCH_2); 5.31 (4H, s, 1- and 1'-CH_2); 5.12 and 5.39 (2H, d, *J* = 14.8, 3- and 3'-CH_2); 7.75 (2H, s, Ar CH); 7.87 (2H, br s, 7- and 7'-Ar CH). ^{13}C NMR spectrum, δ, ppm: 20.00 (4- and 4'-CH_3); 59.36 (OCH_2); 59.52 (OCH_2); 61.50 (NCH_2); 66.32 (3- and 3'-CH_2); 67.36 (1- and 1'-CH_2); 119.52, 126.89; 129.37, 131.05, 131.14, 131.65 and 134.15 (Ar-C). Found, %: Cl 14.45; N 5.84. $C_{28}H_{34}Cl_2N_2O_2$. Calculated, %: Cl 14.17; N 5.59.

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