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STUDY OF THE BEHAVIOR OF *p*-BIS{3-[N,N-DIALKYL-N-(4-HYDROXYBUT-2-YNYL)AMMONIO]PROP-2-YNYL}-BENZENE DICHLORIDES IN RELATION TO AQUEOUS ALKALI. DOUBLE INTRAMOLECULAR RECYCLIZATION OF BENZO[5,6;5',6'-*a,c*]DI(2,2-DIALKYL-4-HYDROXY-METHYL)ISOINDOLINIUM DICHLORIDES

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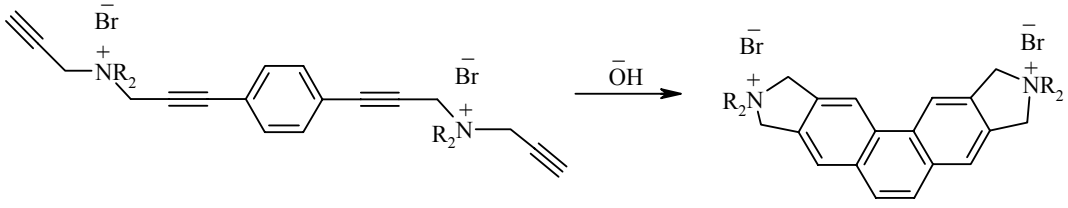
p-Bis{3-[N,N-dialkyl-N-(4-hydroxybut-2-ynyl)ammonio]prop-2-ynyl}benzene dichloride in the presence of catalytic amounts of aqueous alkali is subject to a double intramolecular cyclization forming benzo[5,6;5',6'-a,c]di(2,2-dialkyl-4-hydroxymethyl)isoindolinium dichloride in 40-42% yield. Simultaneously an intramolecular recyclization takes place with the formation of dialkyl(6-dialkylaminomethyl-7,9,10,12-tetrahydro-8,11-dioxadicyclopenta[c,g]phenanthren-1-ylmethyl)amines in 7-9% yield. The same compounds are obtained in 70-72% yield by the recyclization of benzo-[5,6;5',6'-a,c]di(2,2-dialkyl-4-hydroxymethyl)isoindolinium dichlorides under conditions of aqueous alkaline degradation.

Keywords: benzo[5,6;5',6'-*a,c*]di(2,2-dialkyl-4-hydroxymethyl)isoindolinium salts, *p*-bis{3-[N,N-dialkyl-N-(4-hydroxybut-2-ynyl)ammonio]prop-2-ynyl}benzene dichlorides, dialkyl(6-dialkylamino-methyl-7,9,10,12-tetrahydro-8,11-dioxadicyclopenta[*c,g*]-phenanthren-1-ylmethyl)amines, base catalysis, double intramolecular cyclization, intramolecular recyclization.

p-Bis[3-dialkyl-2-propynylammonio-1-propynyl]benzene dibromides under base catalysis conditions undergo a double intramolecular cyclization of the diene synthesis type with the formation of benzo[5,6;5',6'-*a,c*]di(2,2-dialkylisoindolinium dibromides in almost quantitative yield [1].



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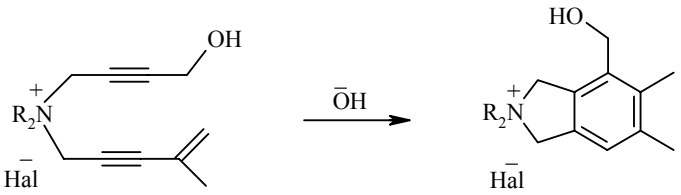
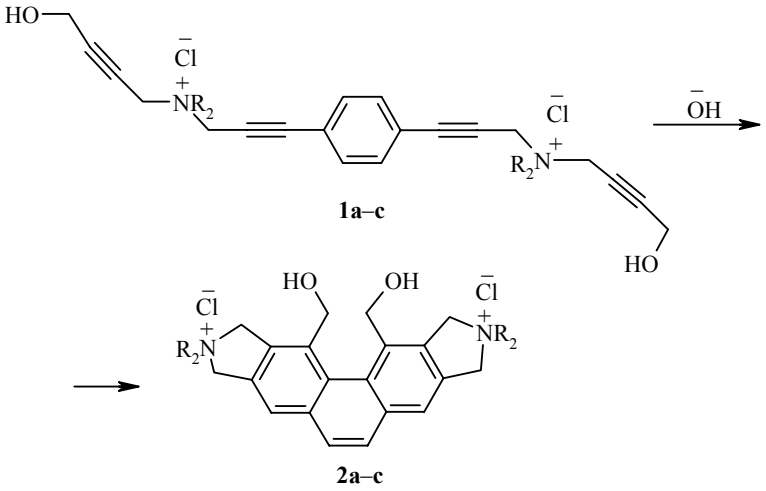
We have established that dialkyl(4-hydroxybut-2-ynyl)(3-alkenyl- or 3-phenylpropargyl)ammonium chloride and bromide salts are smoothly cyclized in the presence of catalytic amounts of aqueous alkali, forming 2,2-dialkyl-4-hydroxymethylisoindolinium and -benz[*f*]isoindolinium salts [2].

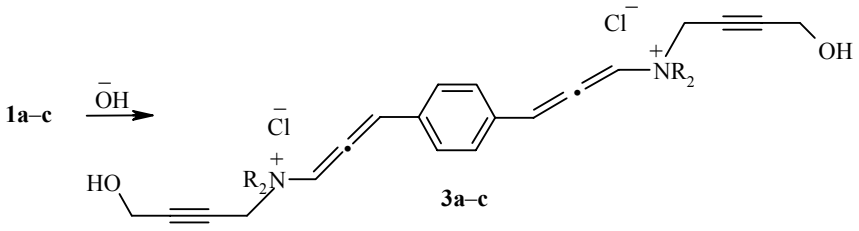


With the aim of clarifying the ability of *p*-bis{3-[N,N-dialkyl-N-(4-hydroxybut-2-ynyl)ammonio]prop-2-ynyl}enzene dichlorides **1a-c** to cyclize and of new potentially bioactive isoindolinium salts to be prepared, the behavior of salts **1a-c** towards catalytic amounts of aqueous alkali was studied. It was shown that salts **1a-c** under base catalysis conditions, unlike the propargyl analogs [1], undergo the double cyclization only by 40-42%, forming benzo[5,6;5',6'-*a,c*]di(2,2-tetramethylene-4-hydroxymethyl)isoindolinium dichloride (**2a**), benzo[5,6;5',6'-*a,c*]di(2,2-pentamethylene-4-hydroxymethyl)isoindolinium dichloride (**2b**), and benzo-[5,6;5',6'-*a,c*]dispiro(4-hydroxymethylisoindoline-2,4'-morpholinium) dichloride (**2c**).



1, **2 a** $R_2 = (–CH_2–)_4$, **b** $R_2 = (–CH_2–)_5$, **c** $R_2 = (CH_2)_2O(CH_2)_2$

Under the same conditions the initial salts **1a-c** are subject to prototropic isomerization by 32-35% with the formation of salts **3a-c** with allenic groupings.



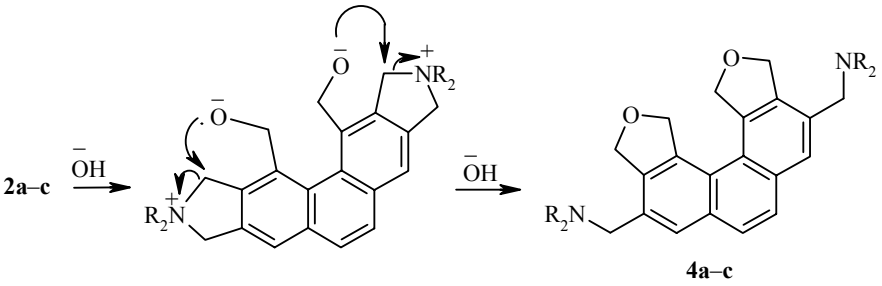
It was shown in a separate experiment that salts **3a-c** are not cyclized in the presence of aqueous alkali, but are polymerized on heating in an alkaline medium. These data point in favor of our assertion [3] that the enyne fragments participate directly in intramolecular cyclization. Salts **2a-c** are readily soluble in water, but

very poorly in alcohol, and are recrystallized from alcohol solution. They do not melt, but are subject to charring. Salts **3a-c** dissolve well both in water and in alcohol.

It is necessary to mention that the cyclization of salts **1a-c**, unlike the propargyl analogs [1], was carried out under the action of 4 N potassium hydroxide solution at a molar ratio of salt to alkali of 2.5:1.

It was shown previously that 2,2-dialkyl-4-hydroxymethylbenz[*f*]isoindolinium and 2,2-dialkyl-4-hydroxymethylisoindolinium chlorides and bromides under conditions of aqueous alkaline degradation are subject to intramolecular recyclization [4, 5]. With the aim of clarifying the ability of salts **2a-c** to enter into intramolecular recyclization their behavior has been studied under conditions of aqueous alkaline degradation. As a fortunate outcome it was possible to develop a practicable means of obtaining potentially bioactive dialkyl(6-dialkylaminomethyl-7,9,10,12-tetrahydro-8,11-dioxadicyclopenta[*c,g*]phenanthren-1-ylmethyl)amines. It is known that the hydrogenated furan ring with a hydrogenated phenanthrene ring enters into the composition of many natural alkaloid molecules.

When studying the aqueous alkaline degradation of salts **2a-c** it became apparent that they, unlike 2,2-dialkyl-4-hydroxymethylbenz[*f*]isoindolinium and 2,2-dialkyl-4-hydroxymethylisoindolinium salts [4, 5], were fairly smoothly recyclized forming (6-pyrrolidin-1-ylmethyl-7,9,10,12-tetrahydro-8,11-dioxadicyclopenta-[*c,g*]phenanthren-1-ylmethyl)pyrrolidine (**4a**), (6-piperidin-1-ylmethyl-7,9,10,12-tetrahydro-8,11-dioxadicyclo-penta[*c,g*]phenanthren-1-ylmethyl)piperidine (**4b**), and (6-morpholinomethyl-7,9,10,12-tetrahydro-8,11-dioxadicyclopenta[*c,g*]phenanthren-1-ylmethyl)morpholine (**4c**) in yields of 70-72%.



4a–c

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

It should be mentioned that amines **4a-c** are formed in 7-9% yield on cyclizing salts **1a-c** under base catalysis conditions. Their picrates gave no depression of melting point with picrates of amines **4a-c** obtained from salts **2a-c** under aqueous alkaline degradation conditions. The hydrochlorides of amines **4a-c** charred on heating above 300°C.

There were characteristic absorption bands in the IR spectra of salts **1a-c** for a disubstituted acetylenic bond at 2230-2240, a hydroxy group at 1030, 1050, 3200-3490, an aromatic ring at 1500, 1600, and 3060, and a *p*-substituted benzene ring at 840 cm^{-1}. In the IR spectra of the cyclization products **2a-c** there were no absorption bands for the disubstituted acetylenic bond and the *p*-substituted benzene ring. There were absorption bands for a 1,2,3,4- and pentasubstituted benzene rings at 800-820 and 870 cm^{-1} respectively. Characteristic absorption bands were also detected in the IR spectra for a hydroxyl group at 1030-1050, 3260-3470 and for an aromatic ring at 1550, 1600, 3060 cm^{-1}.

In the UV spectra of the initial salts **1a-c** conjugation of the benzene ring with the acetylenic bond in the molecule leads to a displacement of the absorption bands characteristic of a benzene ring to the longer wave region of the spectrum (270, 285 nm). As a result of the multiple conjugation absorption bands were displayed in the UV spectra of salts **2a-c** in the longer wave region of the spectrum (308-320 nm)

In the IR spectra of salts **3a-c** characteristic absorption bands were detected for a disubstituted acetylenic bond at 2230, an aromatic ring at 1600, 3030, a *p*-substituted benzene ring at 850, a hydroxyl group at 3200-3490, and an allenic grouping at 1930 cm^{-1}.

TABLE 1. Physicochemical and Spectral Characteristics of Salts **1a-c** and **2a-c***

Compound*[2]	Empirical formula	Found, % / Calculated, %		IR sprctrum, ν, cm^{-1}	UV spectrum, λ_{max}, nm (ε)	Yield, %
		Cl	N			
1a	$C_{28}H_{34}Cl_2N_2O_2$	14.45 / 14.14	5.34 / 5.59	840, 1030, 1050, 1600, 2230, 3060, 3240-3490	270 (4.80), 285 (4.76)	97
1b	$C_{30}H_{38}Cl_2N_2O_2$	13.64 / 13.39	5.04 / 5.29	840, 1030, 1580, 2230, 3050, 3250-3450	240 (4.89), 265 (4.91), 308 (4.32)	95
1c	$C_{28}H_{34}Cl_2N_2O_4$	13.49 / 13.29	5.50 / 5.25	840, 1030, 1050, 1500, 1610, 2240, 3060, 3200-3490	275 (4.80), 285 (4.76)	98
2a	$C_{28}H_{34}Cl_2N_2O_2$	14.42	5.26	800, 870, 1030, 1500, 1600, 3040, 3200-3500	265 (4.60), 308 (4.04), 320 (4.00)	40
2b	$C_{30}H_{38}Cl_2N_2O_2$	13.69	5.54	820, 870, 1050, 1500, 1580, 3040, 3200-3500	265 (4.60), 308 (4.04), 320 (4.00)	40
2c	$C_{28}H_{34}Cl_2N_2O_4$	13.54	5.43	810, 870, 1030, 1580, 1600, 3030, 3050, 3260-3470	263 (4.71) 308 (4.17), 320 (4.00)	42

* Compounds **1a-c** and **2a-c** are isomers.

*[2] Compound **1a** mp 175°C; compound **1b** did not melt, but charred above 250°C; compound **1c** mp 160°C; compounds **2a-c** did not melt, but charred above 300°C.

TABLE 2. Physicochemical and Spectral Characteristics of Amines **4a-c**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	IR spectrum, ν, cm^{-1}	mp of picrate, °C	Yield, %
		C	H	N				
4a	$C_{28}H_{32}N_2O_2$	78.70 / 78.47	7.73 / 7.53	6.30 / 6.54	115	810, 870, 1070, 1140, 1500, 1600, 3060	223	70
4b	$C_{30}H_{36}N_2O_2$	79.16 / 78.91	8.15 / 7.95	5.95 / 6.13	176	820, 870, 1060, 1100, 1550, 1600, 3060	205	72
4c	$C_{28}H_{32}N_2O_4$	73.28 / 73.02	7.21 / 7.00	6.30 / 6.08	160	800, 870, 1030, 1050, 1500, 1610, 2240, 3060, 3200-3490	230	70

In the UV spectra of salts **3a-c** absorption characteristic of the benzene ring was displaced to the longer wavelength region of the spectrum (270, 280 nm) as a result of conjugation.

Characteristic absorption bands were detected in the IR spectra of amines **4a-c** for 1,2,3,4- and pentasubstituted benzene rings at 800-820, 870 cm^{-1} respectively, for an aromatic ring at 1500, 1590, 3060, and for an ether group in a ring at 1060-1140 cm^{-1}.

TABLE 3. ^{1}H NMR Spectra of Salts **1a-c, 2a-c**, and ^{13}C NMR Spectra* of Salts **2a-c**

Com-pound	Chemical shifts, DMSO-d_6, δ, ppm (*J*, Hz)				
	OCH_2	NCH_2	OH (2H)	H_{Ar} (s)	R
1a	4.19 (4H)	4.62 and 4.83 (4H,br)	5.58 (br)	7.69 (4H)	2.17 (8H, m, NCH_2); 3.73 (8H, m, CH_2)
1b	4. 20 (4H, dt, *J* = 5.9, *J* = 1.7)	4.62 and 4.80 (4H,br)	5.49 (t, *J* = 5.9)	7.69 (4H)	1.59 (4H, m, CH_2) and 1.89 (8H, m, CH_2); 3.59 (8H, m, NCH_2)
1c	4.20 (4H,br)	4.79 and 4.97 (4H, br)	5.50 (br)	7.70 (4H)	3.69 (8H, m, OCH_2); 4.02 (8H, m, NCH_2)
2a	4.63 and 4.90 (2H, d, *J* = 12.4)	5.10 and 5.21 (2H,d, *J* = 14.7), 5.12 and 5.28 (2H,d, *J* = 14.7)	5.20 (br)	7.82 and 7.97 (2H)	2.18-2.38 (8H, m, NCH_2); 3.71 (2H, m, CH_2); 3.84 (2H, m, CH_2) and 3.86 (4H, t, *J* = 7.2, CH_2)
2b	4.62 and 4.90 (2H, d, *J* = 12.5)	5.13 and 5.16 (2H,d, *J* = 15), 5.15 and 5.31 (2H,d, *J* = 15)	5.40 (br)	7.81 and 7.96 (2H)	1.68 (4H, m, CH_2); 1.88-2.03 (8H, m, CH_2); 3.67 (8H, m, NCH_2)
2c	4.64 and 4.90 (2H, d, *J* = 12.6)	5.21 and 5.49 (2H,d, *J* = 15), 5.23 and 5.30 (2H,d, *J* = 15)	5.25 (br)	7.83 and 7.99 (2H)	3.73 and 3.82 (4H, m, OCH_2); 4.03-4.14 (8H, m, NCH_2)

* ^{13}C NMR spectrum, δ, ppm: **2a** – 21.40; 21.70; 59.30; 62.80; 63.30; 65.90; 66.50; 120.50; 126.90; 127.10; 132.90; 133.60; 133.70; 136.50; **2b** – 20.70; 20.80; 20.90; 59.30; 59.90; 60.20; 65.90; 66.40; 120.80; 126.90; 127.30; 132.10; 132.70; 133.50; 136.50; **2c** – 58.70; 59.10; 59.30; 61.50; 61.60; 66.30; 66.40; 120.80; 126.90; 127.20; 131.70; 132.30; 133.70; 136.70.

TABLE 4. ^{1}H NMR Spectra of Amines **4b,c**

Compound	Chemical shifts, DMSO-d_6 + CCl_4, δ, ppm (*J*,Hz)				
	NCH_2 (4H)	OCH_2		H_{Ar} (2H, s)	R
		(4H, t, *J* = 2.1)	(4H, t, *J* = 2.1)		
4b	3.63 (s)	5.15	5.28	7.63 and 7.70	1.44 (4H, m, CH_2) and 1.61 (8H, m, CH_2); 2.46 (8H, NCH_2)
4c	3.66 (s)	5.17	5.29	7.64 and 7.70	2.47 (8H, t, *J* = 4.6, NCH_2); 3.64 (8H, t, *J* = 4.6, OCH_2)

The structures of salts **1a-c**, **2a-c**, and amines **4b,c** were also confirmed by ^{1}H NMR spectroscopy. The structures of salts **2a-c** were also established by ^{13}C NMR. The spectra of the compounds indicated above were in agreement with the proposed structures.

EXPERIMENTAL

The IR spectra were taken on a UR 20 spectrometer in KBr disks or in nujol. The UV spectra were taken on a Specord UV-Vis spectrophotometer in ethanol. The ^{1}H and ^{13}C NMR spectra were obtained on a Varian Mercury 300 spectrometer (300 and 75 MHz respectively) at 30°C (303 K), internal standard was TMS.

Salts **1a-c** were obtained in almost quantitative yield by the interaction of *p*-bis[3-dialkylamino-1-propynyl]benzenes [6] with chromatographically pure 1-chloro-4-hydroxy-2-butyne, obtained by the known method of [7], in a benzene–acetonitrile–methanol medium.

The characteristics of salts **1a-c**, **2a-c**, and amines **4a-c** are given in Tables 1 and 2 respectively. Data of ^{1}H NMR spectra of salts **1a-c**, **2a-c** and also of ^{13}C NMR spectra of salts **2a-c** are given in Table 3. Data of ^{1}H NMR spectra of amines **4b,c** are given in Table 4.

Cyclization of Salts 1a-c (General Procedure). A 4 N KOH solution (0.2-0.6 ml) (molar ratio salt–base, 2.5:1) was added to a solution of the initial salt **1a-c** (1.9-6.0 mmol) in water (2-4 ml). The temperature of the reaction mixture rose from 30-50°C during 5-10 min, then a vigorous evolution of heat was observed. The reaction mixture was extracted with ether (2 × 20 ml) to remove products of side reactions. In each case amines **4a-c** (7-9%), identified as picrates, were detected in the ether extract by titration.

On standing fine crystals of salts **2a-c** settled out from the aqueous solution and were filtered off. The mother liquor was acidified with aqueous HCl solution to an acid reaction and the solvent was removed to dryness at low pressure. Salts **3a-c,** formed as a result of prototropic isomerization of salts **1a-c**, were extracted with absolute ethanol.

Aqueous Alkaline Degradation of Salts 2a-c (General Procedure). A fourfold molar amount of KOH (14-22 mmole as appropriate) was added to a solution of salt **2a-c** (3.8-5.6 mmol) in water. The reaction mixture was heated at 90-92°C for 40-60 min, cooled, and the crystals of amines **4a-c** were filtered off, and recrystallized from a hexane–dichloromethane mixture.

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