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SYNTHESIS AND INTRAMOLECULAR RECYCLIZATION OF 2,2-DIALKYL-6-CHLORO-4-HYDROXYMETHYL-BENZO[*f*]ISOINDOLINIUM SALTS

E. O. Chukhajian[1], A. A. Khachatryan[1], A. R. Gevorkyan[1], and G. A. Panosyan[2]

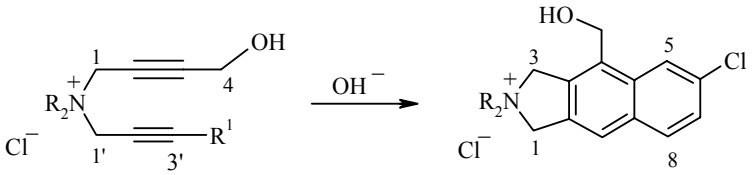
The intramolecular cyclization of dialkyl(2-butynyl-4-hydroxy)[3-(p-chlorophenyl)propargyl]ammonium chlorides, catalyzed by aqueous KOH, was realized. It was shown that the obtained products – 2,2-dialkyl-6-chloro-4-hydroxymethylbenzo[f]isoindolinium chlorides – readily undergo recyclization under the action of a twofold molar amount of KOH in aqueous solution with heating with the formation of 4-dialkylaminomethyl-8-chloro-1,3-dihydronaphtho[1,2-c]furans.

Keywords: dialkyl(2-butynyl-4-hydroxy)[3-(*p*-chlorophenyl)propargyl]ammonium salts, 2,2-dialkyl-6-chloro-4-hydroxymethylbenzo[*f*]isoindolinium salts, base catalysis, recyclization, cyclization.

In the presence of 0.2 mol of aqueous KOH to 1 mol of the initial salt dialkyl(2-butynyl-4-hydroxy)-(3-R^1-propargyl)ammonium salts (R^1 = Ph, vinyl, or isopropyl) undergo cyclization, forming 2,2-dialkyl-4-hydroxymethylisoindolinium and 2,2-dialkyl-4-hydroxymethylbenzo[*f*]isoindolinium salts [1-3].

While studying the question of the stability of the above-mentioned salts under the conditions of aqueous alkaline cleavage we discovered intramolecular recyclization, which included a stage with cleavage of the isoquinoline ring by the action of the alkoxide ion formed in the alkaline medium and the formation of a dihydrofuran ring [2-5]. It was established that the recyclization process was facilitated by increase in the number of aromatic rings and by the presence of a methyl substituent in the benzene ring. Thus, heating of the reaction mass for only 40-60 min is required for the recyclization of benzo[5,6;5′,6′-*a*,*c*]di[2,2-dialkyl-4-hydroxymethyl]isoquinolinium [5].

In order to investigate further the effect of the structure of the initial salts on their cyclization and the subsequent recyclization of the obtained products and also to obtain new potentially active isoindolinium



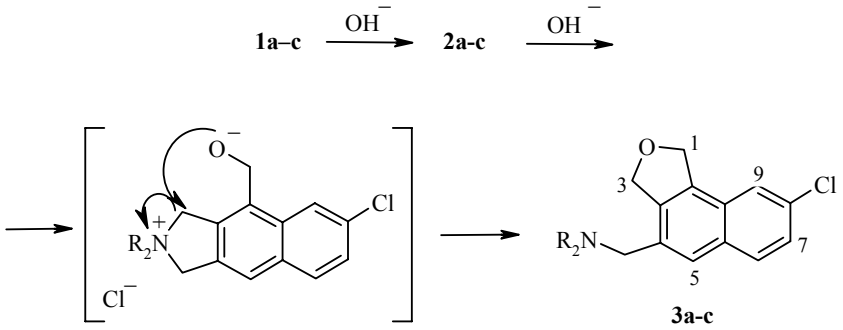
1a-c **2a-c**

1a-c $R^1 = C_6H_4Cl$-*p*, **1**, **2** **a** R = Pr, **b** $R_2 = (CH_2)_5$, **c** $R_2 = (CH_2)_2O(CH_2)_2$

[1]Institute of Organic Chemistry, National Academy of Sciences of the Republic of Armenia; e-mail: hasulik4@mail.ru. [2]Molecular Structure Research Center, National Academy of Sciences of the Republic of Armenia, Erevan 375014; e-mail: henry@msrc.am. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 834-840, June, 2007. Original article submitted June 23, 2006.

derivatives we studied the behavior of dialkyl(4-hydroxy-2-butynyl)[3-(*p*-chlorophenyl)propargyl]ammonium chlorides **1a-c** and their cyclization products **2a-c** under the conditions of base catalysis and aqueous alkaline cleavage respectively.

Like the previously studied analogs (R = Ph, vinyl, or isopropenyl), in the presence of 0.2 mol of aqueous KOH to 1 mol of the salt and after heating at 50-55°C the salts **1a-c** readily undergo cyclization (an exothermic reaction), forming 2,2-dialkyl-6-chloro-4-hydroxymethylbenzo[*f*]isoindolinium chlorides **2a-c** with yields of 60-65%. Here, as before [2-5], the products from recyclization of compounds **2a-c** – 4-dialkylaminomethyl-8-chloro-1,3-dihydronaphtho[1,2-*c*]furans **3a-c** – are also obtained with yields of 10-15%. The latter are formed with yields of 62-68% from the salts **2a-c** by the action of a twofold molar excess of KOH in aqueous solution with heating (80-85°C), and with subsequent cyclization and recyclization without isolation of the salts **2a-c** the total yields of the amines **3a-c** amount to 75-82% [2-4].



3 **a** R = Pr, **b** $R_2 = (CH_2)_5$, **c** $R_2 = (CH_2)_2O(CH_2)_2$

The transformation of the salts **2a-c** into the amines **3a-c** takes 1.0-1.5 h, whereas 2.0-3.5 h is required for the recyclization of the previously investigated 2,2-dialkyl-4-hydroxymethylisoindolinium and 2,2-dialkyl-4-hydroxymethylbenzo[*f*]isoindolinium salts [2, 4]. The ease of recyclization of the salts with substituents in the aromatic ring [3] and the salts with the phenanthrene ring [5] compared with the 2,2-dialkyl-4-hydroxymethylisoindolinium analogs is explained by the higher aromaticity of the benzene ring.

The structure of the synthesized compounds **1a-c** – **3a-c** is confirmed by the results of elemental analysis (Tables 1 and 2), data from the ^1H and ^{13}C NMR spectra (Tables 3-6), and also the IR and UV spectra.

The IR spectra of the initial salts **1a-c** contain absorption bands in the region of 2220-2240 (disubstituted acetylene bond), 1030, 3100-3250 (OH group), 1580, 1600, 3050 (aromatic ring), and 810-840 cm^{-1} (*p*-substituted benzene ring). The above-mentioned absorption of the disubstituted acetylene bond and the *p*-substituted benzene ring is not observed in the spectra of the cyclization products, but there are absorption bands at 1040, 1080, 3200-3500 (OH group), 1580, 1600, 3130-3150 (aromatic ring), and 820 and 880 cm^{-1} (1,2,4- and pentasubstituted benzene rings respectively).

In the IR spectra of the amines **3a-c** there is absorption at 1580, 3000, and 3040 (aromatic ring), 1030 and 1070 (CH_2OCH_2 group), and 830 and 870 cm^{-1} (1,2,4- and pentasubstituted benzene rings respectively).

The IR spectra of the initial salts **1a-c** contain an absorption maximum characteristic of the benzene ring at 255 nm, which is shifted in the spectra of the cyclic salts **2a-c** toward the long-wave region (275, 285, 300 nm) due to the presence of the naphthalene fragment.

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

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	Compound*	Found, %		mp, °C	Yield, %
		Cl	N			Cl	N		
1a	$C_{19}H_{25}Cl_2NO$	20.45 / 20.01	3.77 / 3.95	106-107	**2a**	20.39	3.69	—*[2]	60
1b	$C_{18}H_{21}Cl_2NO$	21.31 / 20.96	4.44 / 4.14	175-176	**2b**	20.59	3.95	280-281	62
1c	$C_{17}H_{19}Cl_2NO_2$	20.48 / 20.84	4.40 / 4.12	200-202	**2c**	20.45	4.30	252-253	65

* The empirical formulas of the salts **2a-c** coincide with the empirical formulas of the corresponding initials salts **1a-c**.
*[2] The salt was not obtained in the crystalline form.

TABLE 2. Physicochemical Characteristics of Amines **3a–c**

Compouna	Empirical formula	Found, % / Calculated, %				mp, °C	mp picrate, °C	mp chlorohydrate,°C	Yield, %
		C	H	Cl	N				
3a	$C_{19}H_{24}ClNO$	71.33 / 71.81	7.82 / 7.56	10.95 / 11.18	4.59 / 4.41	—*	190-192	171-172	75
3b	$C_{18}H_{20}ClNO$	71.21 / 71.64	6.88 / 6.63	12.04 / 11.77	4.42 / 4.64	84-85	191-192	251-252	78
3c	$C_{17}H_{18}ClNO_2$	67.70 / 67.22	5.61 / 5.93	12.05 / 11.70	4.38 / 4.61	160-161	208-209	214-216	82

* mp 180-182°C (2 mm Hg).).

TABLE 3. ^{1}H NMR Spectra of Salts **1a-c**

Compound	Chemical shifts, δ, ppm. (*J*, Hz)						
	$C_{(1)}H_2$	$C_{(4)}H_2$	$C_{(1')}H_2$, s	OH, br. s	C_6H_4Cl-*p*		R
					2H-*o*, d	2H-*m*, d	
1a	4.63 (br. t, *J* = 1.9)	4.17 (br. s)	4.92	5.73	7.59 (*J* = 8.5)	7.38 (*J* = 8.5)	1.05 (6H, t, *J* = 7.2, $2CH_3$); 1.87 (4H, m, $2\underline{CH_2}CH_3$); 3.58 (4H, m, $2NCH_2$)
1b	4.73 (br. s)	4.18 (s)	5.00	5.60	7.62 (*J* = 8.3)	7.38 (*J* = 8.3)	1.73 (2H, m, $N(CH_2)_2\underline{CH_2}$); 1.96 (4H, m, $2NCH_2\underline{CH_2}$); 3.82 (4H, br. t, *J* = 5.5, $2NCH_2$)
1c	4.83 (br. t, *J* = 1.9)	4.18 (br. s)	5.05	5.51	7.64 (*J* = 8.5)	7.43 (*J* = 8.5)	3.77 (4H, m, $2OCH_2$); 4.03 (4H, m, $2NCH_2$)

TABLE 4. ^{1}H NMR Spectra of Salts **2b,c**

Compound	Chemical shifts, δ, ppm (*J*, Hz)							
	$C_{(1)}H_2$, s	$C_{(3)}H_2$, s	CH_2O	H-5, d	H-7, dd	H-8	OH	R
2b	5.07	5.25	4.93 (d, *J* = 5.7)	8.21 (*J* = 2.1)	7.59 (J_1 = 8.8, J_2 = 2.1)	8.03 (d, *J* = 8.8), 7.93 (br. s)	5.81 (t, *J* = 5.7)	1.64 (2H, br. q, *J* = 6.0, $N(CH_2)_2\underline{CH_2}$); 1.81-2.01 (4H, m, $2NCH_2\underline{CH_2}$); 3.60 (4H, t, *J* = 5.7, $2NCH_2$)
2c	5.20	5.38	4.94 (br.)	8.22 (*J* = 2.1)	7.60 (J_1 = 8.7, J_2 = 2.1)	8.05 (d, *J* = 8.7), 7.95 (br. s)	5.77 (br. s)	3.70 (4H, t, *J* = 4.8, $2OCH_2$); 3.97-4.12 (4H, m, $2NCH_2$)

TABLE 5. ^{1}H NMR Spectra of Amines **3a-c**

Compound	Chemical shifts, δ, ppm. (*J*, Hz)							
	NCH_2, s	$C_{(1)}H_2$, t	$C_{(3)}H_2$, t	H-5, s	H-6, d	H-7, dd	H-9 (d, *J* = 2.1)	R
3a	3.59	5.23 (*J* = 3.0)	5.34 (*J* = 3.0)	7.61	7.81 (*J* = 8.7)	7.37 (J_1 = 8.7, J_2 = 2.1)	7.56	0.85 (6H, t, *J* = 7.3, $2CH_3$); 1.47 (4H, sext, *J* = 7.3, $2\underline{CH_2}CH_3$); 2.36(4H, t, *J* = 7.3, $2NCH_2$)
3b	3.51	5.24 (*J* = 3.0)	5.35 (*J* = 3.0)	7.59	7.82 (*J* = 8.8)	7.38 (J_1 = 8.8, J_2 = 2.1)	7.57	1.45 (2H, m, $N(CH_2)_2\underline{CH_2}$); 1.56 (4H, m, $2NCH_2$); 2.37 (4H, t, *J* = 5.1, $2NCH_2\underline{CH_2}$)
3c	3.60	5.26 (*J* = 1.0)	5.36 (*J* = 1.0)	7.62	7.84 (*J* = 8.8)	7.39 (J_1 = 8.8, J_2 = 2.1)	7.58	2.41 (4H, m, $2NCH_2$); 3.60 (4H, m, $2OCH_2$)

TABLE 6. ^{13}C NMR Spectra of Salts **1b, 2b**,**c** and Amines **3b,c**

Compound	Chemical shifts, δ, ppm. (*J*, Hz)
1b	19.29 ($NCH_2\underline{CH_2}$); 20.21 ($N(CH_2)_2\underline{CH_2}$); 48.85 ($N\underline{CH_2}CH_2$); 49.88 ($C_{(1)}$ and $C_{(1')}$); 57.10 (CH_2OH); 71.24 ($C_{(3)}$); 77.82 ($C_{(3')}$); 89.22 ($C_{(2)}$); 92.20 ($C_{(2')}$); 119.13 ($C_{(4')}$); 128.21 ($C_{(6')}$ and $C_{(8')}$); 133.26 ($C_{(5')}$ and $C_{(7')}$); 134.57 ($C_{(9')}$)
2b	20.60 ($N(CH_2)_2\underline{CH_2}$); 20.74 ($NCH_2\underline{CH_2}$); 57.90 ($CH_2OH$); 59.95 ($N\underline{CH_2}CH_2$); 66.35 ($C_{(3)}$); 66.00 ($C_{(1)}$); 121.88, 123.29, 126.73, 130.54, 130.98, 131.35, 131.70, 131.73, 131.76, 131.76 and 132.69 (Ar)
2c	20.60 ($N(CH_2)_2\underline{CH_2}$); 20.74 ($NCH_2\underline{CH_2}$); 57.90 ($CH_2OH$); 59.95 ($N\underline{CH_2}CH_2$); 66.35 ($C_{(3)}$); 66.00 ($C_{(1)}$); 121.88, 123.29, 126.73, 130.54, 130.98, 131.35, 131.70, 131.73, 131.76, 131.76 and 132.69 (Ar)
3b	23.79 ($N(CH_2)_2\underline{CH_2}$); 25.41 ($NCH_2\underline{CH_2}$); 53.87 ($N\underline{CH_2}CH_2$); 61.51 ($NCH_2Ar$); 72.08 and 73.47 ($OCH_2$); 122.07, 125.68, 126.45, 126.84, 129.36, 130.76, 130.94, 133.90 and 137.46 (Ar)
3c	53.03 ($N\underline{CH_2}CH_2$); 61.22 (NCH_2Ar); 65.98 ($O\underline{CH_2}CH_2$); 72.12 and 73.42 (OCH_2Ar); 122.10, 125.80, 126.72, 126.92, 129.38, 130.47, 130.71, 131.12, 134.06 and 137.37 (Ar)

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer in tablets with KBr or in vaseline oil. The UV spectra were recorded on a Specord UV-Vis spectrometer in ethanol. The ^{1}H and ^{13}C NMR spectra were obtained for solutions in DMSO-d_6 + CCl_4 on a Varian Mercury-300 spectrometer (300 and 75 MHz respectively at 30°C (303 K)) with TMS as internal standard. The purity of the salts **1a-c** and **2a-c** was checked by TLC on Silufol UV-254 plates in the 8:2:3:1 *n*-butanol–ethanol–water–acetic acid solvent system with development in iodine vapor. The signals in the ^{1}H and ^{13}C NMR spectra of the salts **2a-c** and the amines **3a-c** were assigned on the basis of the 2D COSY, NOESY, and HMQC spectra. The initial salts **1a-c** were obtained with almost quantitative yields by the reaction of the corresponding 1,1-dialkyl-3-(*p*-chlorophenyl)-propargylamines **4a-c** [6] in acetonitrile with chromatographically pure 1-chloro-4-hydroxy-2-butyne, synthesized by the known method [7].

The previously undescribed **3-(*p*-Chlorophenyl)-1,1-dipropylpropargylamine** (**4a**) was obtained by the reaction of dipropylamine (6.6 g, 66 mmol), paraform (2.1 g, 70 mmol) and *p*-chlorophenylacetylene (9.0 g, 66 mmol) in dioxane (150 ml) in the presence of ferric chloride (0.1 g) and cupric acetate (0.1 g). The amine **4a** was obtained by the usual treatment [3]. Yield 64%; bp 125-126°C (2 mm Hg), mp of picrate 153-155°C (ethanol), mp of chlorohydrate 142-143°C. Found, %: C 71.67; H 8.29; C1 14.55; N 5.33. $C_{15}H_{20}ClN$. Calculated, %: C 72.14; H 8.02; Cl 14.23; N 5.61.

Cyclization of Salts 1a-c. 2,2-Dialkyl-6-chloro-4-hydroxymethylbenzo[*f*]isoindolinium Chlorides 2a-c (General Method). To a solution of the salt **1a-c** (5.8-10.00 mmol) in water (3-4 ml) we added a 2N solution of KOH (0.6-1.0 ml) (molar ratio of salt and base 5:1). The reaction mixture was heated at 50-55°C and kept at this temperature for 5-10 min until the exothermic reaction started. The heating was then stopped, and the temperature of the reaction mixture increased spontaneuosly till 80-85°C and then reduced gradually to room temperature. The solidified reaction mass was extracted with a 4:1 mixture of ether and dichloromethane (3×25 ml) to remove the products of side reactions. In the extract in each case 10-15% of the amine **3a-c** was detected by titration; its picrate did not give a melting point depression with the picrate of the amine **3a-c** prepared under the conditions for the recyclization of the salts **2a-c** (see below). In the case of the salt **1a** the aqueous solution after extraction was acidified with hydrochloric acid, and the solvent was evaporated to dryness. The salt **2a** was extracted from the residue with absolute ethanol, precipitated with absolute ether, and filtered off. The salts **2b,c** after cyclization fall out and are filtred off.

Recyclization of the Salts 2a-c. 8-Chloro-4-dialkylaminomethyl-1,3-dihydronaphtho[1,2-*c*]furans 3a-c (General Method). A. To a solution of the salt **2a-c** (5-8 mmol) in water (3-5 ml) we added twice the molar amount of KOH. The mixture was kept at 80-85°C for 1-1.5 h. The solidified reaction mixture was extracted with a 1:5 mixture of dichloromethane and ether (3×30 ml). The extract was washed with water, dried with magnesium sulfate, and evaporated. The residue was the amine **3b**,**c** and was recrystallized from a 3.3:1 mixture of ether and dichloromethane or a 2.5:1 mixture of hexane and dichloromethane. The amine **3a** does not crystallize.

B. The salts **1a-c** underwent cyclization under the conditions of base catalysis (see above). Twice the molar amount of KOH (to 1 mol of the salt **1**), dissolved in water (2-3 ml), was then added to the reaction mass without isolation of the products **2a-c**, and the obtained mixture was kept at 80-85°C for 1-1.5 h. The solidified reaction mixture was then treated according to method A.

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