Chemistry of Heterocyclic Compounds, Vol. 40, No. 2, 2004

CYCLIZATION OF DIALKYL-(4-HYDROXY-2-BUTYNYL)(3-ALKENYL-PROPARGYL)AMMONIUM SALTS AND RECYCLIZATION OF THE 2,2-DIALKYL-4-HYDROXYMETHYLISOINDOLINIUM SALTS OBTAINED

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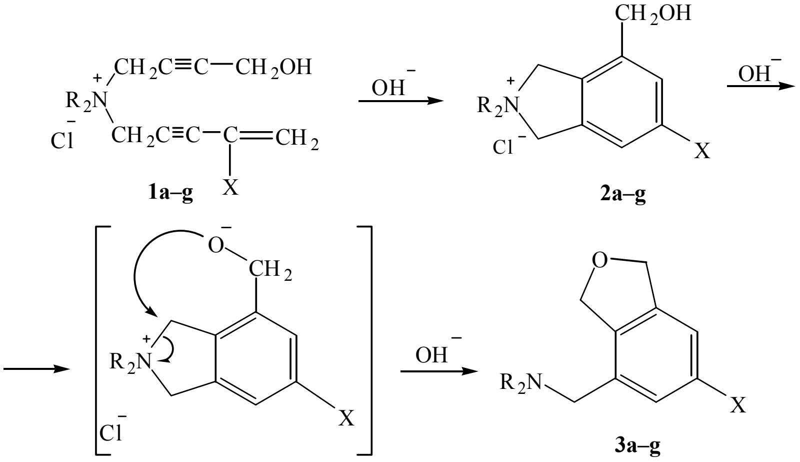
2,2-Dialkyl-4-hydroxymethylisoindolinium chlorides, like benzisoindolinium salts, readily undergo intramolecular recyclization under conditions of aqueous alkaline decomposition, comprising fission of the isoindolinium ring and formation of a dihydrofuran ring leading to (1,3-dihydro-4-isobenzofuranylmethyl)dialkylamines.

Keywords: 4-hydroxy-2-butynyl group, dialkyl(3-alkenylpropargyl)-(4-hydroxybutyn-2-yl)ammonium salts, (1,3-dihydro-4-isobenzofuranylmethyl)dialkylamines, base catalysis, recyclization, cyclization.

Chloride and bromide salts of dialkyl(4-hydroxy-2-butynyl)(3-alkenylpropargyl)ammonium of type **1** and of -(3-phenylpropargyl)ammonium undergo intramolecular cyclization in the presence of catalytic amounts of aqueous alkali with the formation of 2,2-dialkyl-4-hydroxymethylisoindolinium salts **2** and -benz[*f*]iso-indolinium salts [1]. When studying the aqueous alkaline decomposition of 2,2-dialkyl-4-hydroxymethylbenz-



1a, 2a, 3a; **1b, 2b, 3b** R = Et; **1c, 2c, 3c** R = Pr; **1d, 2d, 3d** R = Bu;
1e, 2e, 3e $R_2 = (–CH_2–)_4$; **1f, 2f, 3f** $R_2 = (–CH_2–)_5$, **1g, 2g, 3g** $R_2 = (CH_2)_2O(CH_2)_2$
In all cases X = H, **1b**, **2b**, **3b** X = Me

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TABLE 1. Physicochemical Characteristics and Yields of Amines **3a-g**

Com-pound	Empirical formula	Found, % Calculated, %			Bp., °C (mm Hg.) mp, °C	n_D^{20}	Mp picrate, °C (ethanol)	Mp hydrochloride, °C (abs. ethanol)	IR spectrum, ν, cm^{-1}	Yield, %
		C	H	N						
3a	$C_{13}H_{19}NO$	76.38 76.06	9.47 9.33	6.05 6.82	110 (2)	1.5238	137	140-141	705, 760, 1050, 1200, 1550, 1600, 3030	61
3b	$C_{14}H_{21}NO$	76.97 76.67	9.02 9.65	6.60 6.39	114 (2)	1.5290	*	*2	840, 1030-1070, 1200, 1590, 1600	64
3c	$C_{15}H_{23}NO$	77.56 77.21	9.83 9.93	6.25 6.00	140 (1)	1.5110	145-146	152-154	705, 770, 1050, 1200-1240, 1540, 1590, 3040	59
3d	$C_{17}H_{27}NO$	78.44 78.11	10.60 10.41	5.07 5.36	82 (1)	1.5070	*	*2	700, 770, 1050, 1200, 1550, 1600, 3040	60
3e	$C_{13}H_{17}NO$	77.10 76.81	8.68 8.43	7.04 6.89	107 (1)	1.5440	155	193	705, 770, 1050, 1200-1240, 1540, 1590, 3040	60
3f	$C_{14}H_{19}NO$	77.73 77.38	9.06 8.81	6.23 6.45	127 (1)	1.5410	186-187	224-225	700, 750-770, 1050, 1200, 1550, 1600, 3040	68
3g	$C_{13}H_{17}NO_2$	71.57 71.21	7.56 7.81	6.14 6.39	145 (2) 50-51 (hexane)	—	174-175	194-195	705, 760, 1050, 1200, 1550, 1590, 3050	69

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* No picrate formed.

*2 Hygroscopic.

TABLE 2. Physicochemical Characteristics of Amines **4c,d,f** and Salts **1c,d,f,g**

Compound	Empirical formula	Found, % Calculated, %				Bp, °C (mm Hg)	n_D^{20}	Mp hydrochloride, °C (abs. ethanol)	Yield, %
		C	H	Cl	N				
4c	$C_{11}H_{19}N$	80.24 79.94	11.84 11.59		8.26 8.47	64-65 (3)	1.4662	*[2]	58
4d	$C_{13}H_{23}N$	81.21 80.76	12.29 11.99		6.92 7.25	84 (3)	1.4690	83	55
4f	$C_{10}H_{15}N$	80.85 80.48	10.36 10.13		9.70 9.39	83-85 (2)	1.5020	137-138	58
1c	$C_{15}H_{24}ClNO$	67.02 66.77	9.12 8.97	13.48 13.14	4.98 5.19	*			~100
1d	$C_{17}H_{28}ClNO$	68.75 68.5	9.65 9.47	11.58 11.90	4.96 4.70	*			~100
1f	$C_{14}H_{20}ClNO$	66.51 66.26	8.14 7.94	13.62 13.97	5.77 5.52	*			~100
1g	$C_{13}H_{18}ClNO_2$	61.33 61.05	7.30 7.09	13.53 13.86	5.50 5.48	*			~100

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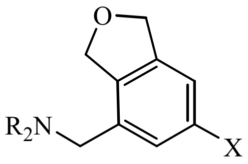
* Salts **1c,d,f,g** were honey-like.

*[2] Salts were hygroscopic.

TABLE 3. ^{1}H NMR Spectra of Amines **3a-g** in DMSO-d_6+CCl_4, δ, ppm, Coupling Constants (*J*, Hz)



3b* R = C_2H_5, X = CH_3;
3a, c–g R = C_2H_5, C_3H_7, C_4H_9, $(CH_2)_4$, $(CH_2)_5$, $(CH_2)_2O(CH_2)_2$,
X = H

Compound	N–CH_2, s	H_2C–O–CH_2, t	H_{Ar}, m	R
3a	3.46	4.97, 5.03, *J* = 2.2	7.05-7.15	1.01 (6H, t, *J* = 7.2, $2CH_3$); 2.45 (4H, q, *J* = 7.2, $2CH_2$)
3c	3.44	4.98, 5.02, *J* = 2.3	7.06-7.17	0.85 (6H, t, *J* = 7.3, $2CH_3$); 1.45 (4H, m, $2CH_3\underline{CH_2}$); 2.32 (4H, t, *J* = 7.3, $N(CH_2)_2$)
3d	3.43	4.99, 5.02, *J* = 2.3	7.05-7.17	0.87 (6H, t, *J* = 7.2, $2CH_3$); 1.27 (4H, m, $2CH_3\underline{CH_2}$); 1.41 (4H, m, $2CH_3CH_2\underline{CH_2}$); 2.34 (4H, t, *J* = 7.1, $N(CH_2)_2$)
3e	3.52	4.99, 5.02, *J* = 2.3	7.05-7.17	1.70-1.80 (4H, m, $2CH_2$); 2.41-2.48 (4H, m, $N(CH_2)_2$)
3f	3.36	4.98, 5.03, *J* = 2.3	7.06-7.16	1.44 (2H, m, CH_2); 1.55 (4H, quintet, *J* = 5.1, $2CH_2$); 2.32 (4H, t, *J* = 5.1, $N(CH_2)_2$)
3g	3.41	5.00, 5.05, *J* = 2.2	7.05-7.20	2.36 (4H, m, $N(CH_2)_2$); 3.59 (4H, m, $O(CH_2)_2$)

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* ^{1}H NMR spectrum of amine **3b** ($CDCl_3$), δ, ppm (*J*, Hz): 1.03 (6H, t, *J* = 7.2, $2CH_3$); 2.36 (3H, s, CH_3); 2.48 (4H, q, *J* = 7.2, $2CH_2$); 3.45 (2H, s, NCH_2); 5.08 (2H, br. s, OCH_2); 5.14 (2H, br. s, OCH_2); 6.92 and 7.01 (2H, br. s, H_{Ar}).

^{13}C NMR spectrum of amine **3f** (DMSO-d_6+CCl_4), δ, ppm: 23.90 (CH_2); 25.49 ($2CH_2$); 53.90 [$N(CH_2)_2$]; 61.38 (NCH_2); 72.04 (OCH_2); 72.34 (OCH_2); 118.76, 126.52, and 126.81 ($3CH_{Ar}$); 132.41, 137.99, and 138.83 ($3C_{Ar}$).

^{13}C NMR spectrum of amine **3g** (DMSO-d_6+CCl_4), δ, ppm: 52.98 [$N(CH_2)_2$]; 60.91 (NCH_2); 65.94 [$O(CH_2)_2$]; 71.93 (OCH_2); 72.31 (OCH_2); 118.97, 126.49, and 126.92 ($3CH_{Ar}$); 131.25, 137.99, and 138.86 ($3C_{Ar}$).

[*f*]isoindolinium chlorides and bromides it was discovered that intramolecular recyclization occurred [2]. With the aim of establishing the general nature of this reaction, the behavior of 2,2-dialkyl-4-hydroxymethyl-isoindolinium salts under conditions of aqueous alkaline decomposition has been studied in the present work.

Since salts **2a-g**, formed by the cyclization of dialkyl(4-hydroxy-2-butynyl)(3-alkenylpropargyl)-ammonium salts **1a-g**, are not successfully obtained in the crystalline state, we studied their decomposition without isolating them.

The recyclization of salts **2a-g**, unlike the benzisoindolinium analogs, is effected on extended heating. The recyclization products, (1,3-dihydro-4-isobenzofuranylmethyl)dialkylamines **3a-g**, were obtained in 60-68% yield (Table 1). Based on the investigations carried out it may be said that the intramolecular recyclization detected by us in [2] has a general character and opens broad possibilities for making potentially bioactive amines containing a dihydrofuran ring. The hydrogenated furan ring is found in the composition of many natural alkaloids. Amines **3a-g** were also obtained in 5-10% yield on cyclization of salts **1a-g** under base catalyzed conditions.

In the IR spectra of the initial dialkyl(3-vinylpropargyl)amines **4c,d,f,** synthesized for the first time, there were characteristic absorption bands for a doubly substituted acetylenic bond at 2220-2230, for $-CH=CH_2$ at 920, 930, and a conjugated C=C bond at 1580-1610 cm^{-1} (Table 2).

In the IR spectra of the initial salts **1c,d,f,g**, which have been obtained for the first time, characteristic absorption bands were detected for a doubly substituted acetylenic bond at 2220, for a hydroxyl group at 1020 and 3200-3400, for $-CH=CH_2$ at 920, 930, and also for a conjugated C=C bond at 1580-1610 cm^{-1} (Table 2).

In the IR spectra of amines **3a-g** absorption bands were detected characteristic of 1,2,3- and 1,2,3,5-substituted benzene rings at 700 and 760, and at 840 cm^{-1} respectively, for the aromatic ring at 1550, 1600, and 3050, and for an ether grouping at 1050 and 1200 cm^{-1}. The structures of amines **3a-g** were confirmed by ^1H NMR spectroscopy, and the structures of **3f,g** also by the ^{13}C NMR method (Table 3). The spectra of the compounds indicated were in agreement with the proposed structures.

EXPERIMENTAL

The IR spectra were taken on a UR 20 spectrometer in KBr disks or in nujol mulls. The ^1H and ^{13}C NMR spectra were obtained on a Varian Mercury 300 spectrometer (300 MHz for proton and 75 MHz for carbon nuclei) at 30°C (303 K). Internal standard was TMS.

The initial dialkyl(3-alkenylpropargyl)amines were synthesized by the Mannich reaction [3]. Salts **1a-g** were obtained in quantitative yield in acetonitrile by the interaction of dialkyl(3-alkenylpropargyl)amines **4a-g** with chromatographically pure 1-chloro-4-hydroxy-2-butyne obtained by the procedure of [4].

The characteristics of amines **3a-g** and the data of ^1H and ^{13}C NMR spectra are given in Tables 1 and 3. The characteristics of amines **4c,d,f** and of salts **1c,d,f,g** are given in Table 2.

Cyclization of Salts 1a-g and the Direct Aqueous Alkaline Decomposition of Salts 2a-g (General Method). A 2N KOH solution (1.8 ml) was added to a solution of the initial salt **1a-g** (18 mmol) (molar ratio salt : base = 5 : 1). The reaction mixture was heated at 50-55°C for 5-10 min, then self-heating of the reaction mixture occurred to 75-85°C. The reaction mixture was extracted with ether (2 × 30 ml) to remove products of side reactions. In each case amines **3a-g** (5-10%) were detected in the ether extract by titration, the picrates of which gave no depression of melting point with picrates of amines **3a-g** obtained on aqueous alkaline decomposition of salts **2a-g**. A twofold molar quantity of potassium hydroxide dissolved in water (2-3 ml) was then added to the reaction mixture without isolating the cyclization products **2a-g**. The reaction mixture was boiled for 3-3.5 h at 85-90°C. The mixture was extracted with ether (3 × 50 ml), the ether extract was washed with water, and dried over $MgSO_4$. After removing the ether, amines **3a-g** were obtained by vacuum distillation.

REFERENCES

1. E. O. Chukhadzhyan, A. R. Gevorkyan, El. O. Chukhadzhyan, K. G. Shakhatuni, F. S. Kinoyan, and G. A. Panosyan, *Khim. Geterotsikl. Soedin.*, 34 (2004).
2. E. O. Chukajian, H. R. Gevorkyan, E. O. Chukhajian, K. G. Shakhatuni, H. A. Panosyan, and R. A. Tamazyan, *J. Heterocycl. Chem.*, **40**, 1059 (2003).
3. E. O. Chukhadzhyan, A. R. Gevorkyan, El. O. Chukhadzhyan, and K. G. Shakhatuni, *Zh. Org. Khim.*, **36**, 9 (2000).
4. G. Dupont, R. Dulou, and G. Lefebvre, *Bull. Soc. Chem. France*, 816 (1954).