

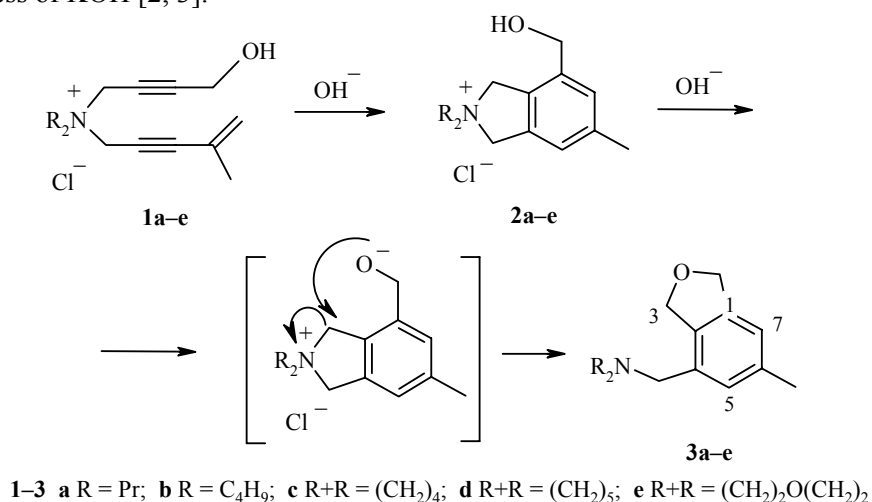
## CYCLIZATION OF DIALKYL(4-HYDROXY-2-BUTYNYL)- (3-ISOPROPENYLPROPARGYL)AMMONIUM SALTS AND INTRAMOLECULAR RECYCLIZATION OF THE RESULTANT PRODUCTS

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*2,2-Dialkyl(4-hydroxy-2-butynyl)(3-isopropenylpropargyl)ammonium chlorides in the presence of 0.2 molar equivalents of KOH in water undergo facile cyclization to give 2,2-dialkyl-4-hydroxymethyl-6-methylisobenzofuranylamine chlorides, which cyclize to dialkyl(6-methyl-1,3-dihydro-4-isobenzofuranylmethyl)amines by the action of a two-fold molar excess of KOH in water.*

**Keywords:** dialkyl(4-hydroxy-2-butynyl)(3-isopropenylpropargyl)ammonium salts, dialkyl(6-methyl-1,3-dihydro-4-isobenzofuranylmethyl)amines, intramolecular cyclization, base catalysis, recyclization.

In previous work [1, 2], we showed that dialkyl(4-hydroxy-2-butynyl)(3-phenylpropargyl)ammonium chlorides and bromides or dialkyl(4-hydroxy-2-butynyl)(3-vinylpropargyl)ammonium chlorides and bromides cyclize under base catalysis conditions to give 2,2-dialkyl-4-hydroxymethylbenz[*f*]isobenzofuranylamine or 2,2-dialkyl-4-hydroxymethylisobenzofuranylamine salts, respectively. The intramolecular recyclization of these salts was discovered in a study of the stability of these products under aqueous alkaline cleavage conditions using a twofold molar excess of KOH [2, 3].



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TABLE 1. Characteristics of Salts **1a-e**\*

Com pound	Empirical formula	Found, %		IR spectrum, $\nu$ , $\text{cm}^{-1}$	UV spectrum, $\lambda_{\text{max}}$ , nm
		Calculated, %			
		Cl	N		
<b>1a</b>	C <sub>16</sub> H <sub>26</sub> ClNO	$\frac{12.21}{12.52}$	$\frac{4.65}{4.94}$	890, 1020, 1580, 2230, 3200-3450	225
<b>1b</b>	C <sub>18</sub> H <sub>30</sub> ClNO	$\frac{11.11}{11.39}$	$\frac{4.19}{4.49}$	890, 1030, 1600, 2240, 3200-3500	220
<b>1c</b>	C <sub>14</sub> H <sub>20</sub> ClNO	$\frac{14.28}{14.00}$	$\frac{5.27}{5.52}$	890, 1020, 1580, 2230, 3200-3400	225
<b>1d</b>	C <sub>15</sub> H <sub>22</sub> ClNO	$\frac{13.62}{13.27}$	$\frac{5.52}{5.23}$	890, 1020, 1600, 2240, 3200-3500	220
<b>1e</b>	C <sub>14</sub> H <sub>20</sub> ClNO <sub>2</sub>	$\frac{12.88}{13.17}$	$\frac{4.94}{5.19}$	890, 1030, 1580, 2230, 3300-3500	230

\* Salts **1a-e** are hygroscopic

In a continuation of these studies, we investigated the cyclization of dialkyl(4-hydroxy-2-butynyl)(3-isopropenylpropargyl)ammonium chlorides **1a-e**, which are analogs of the salts with a vinylpropargyl substituent [2], and the recyclization of the resultant products **2a-e**.

We found that salts **1a-e** undergo facile, exothermic cyclization in aqueous KOH (with a 5:1 salt-base ratio) to give salts **2a-e**. Analytical samples of salts **2a-e** could not be obtained due to their hygroscopicity. Thus, the recyclization of these products by the action of a twofold molar excess of KOH at 85-90°C was studied without their separation from the reaction mixture. The recyclization gave the corresponding dialkyl(6-methyl-1,3-dihydro-4-isobenzofuranylmethyl)amines **3a-e**, which are already formed in 12-15% yield in the cyclization of **1a-e** under base catalysis conditions. The overall yields of amines **3** are 72-81%. We should note that the recyclization of salts **2a-e** requires only 2.0-2.5 h in contrast to the recyclization of their analogs not containing a methyl substituent in the benzene ring, which requires 3.0-3.5 h [2].

The study of the biological activity of amines **3a-e** would hold considerable interest since the hydrogenated furan ring is a fragment in many natural alkaloids and important drugs.

The structure and composition of salts **1a-e** and amines **3a-e** were supported by the elemental analysis data as well as the IR spectra (Tables 1 and 2) and the <sup>1</sup>H and <sup>13</sup>C NMR spectra (Table 3).

## EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer for samples in KBr pellets or vaseline mull. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were taken on a Varian Mercury-300 spectrometer at 300 and 75 MHz, respectively, at 30°C (303K) for samples in DMSO-d<sub>6</sub>+CCl<sub>4</sub> with TMS as the internal standard.

Salts **1a-e** were obtained in quantitative yield by the reaction of the corresponding dialkyl(3-isopropenylpropargyl)amines **4a-e** with chromatographically pure 1-chloro-4-hydroxy-2-butyne [4] in acetonitrile.

Starting amines **4a-e** were prepared by the Mannich reaction [5].

Previously unreported **1,1-dipropyl(3-isopropenylpropargyl)amine (4a)** was obtained by the reaction of dipropylamine (50.5 g, 0.5 mol), paraformaldehyde (15.0 g, 0.5 mol), and isopropenylacetylene (39.6 g, 0.6 mol) in dioxane (150 ml) in the presence of ferric chloride (0.1 g) and cupric acetate (0.1 g). The reaction mixture was maintained for 70 h at 90-95°C, cooled, and made acidic by adding hydrochloric acid. A portion of the solvent was distilled off under reduced pressure. The residue was made basic by adding alkali and extracted

TABLE 2. Physicochemical Characteristics and Yields of Amines **3a-e**

Com- pound	Empirical formula	Found, %			Bp, °C (Hg mm.)	$n_D^{20}$	IR spectrum, $\nu$ , $\text{cm}^{-1}$	mp of picrate, °C	Overall yield, %
		C	H	N					
<b>3a</b>	$\text{C}_{16}\text{H}_{25}\text{NO}$	$\frac{77.17}{77.73}$	$\frac{10.49}{10.12}$	$\frac{5.34}{5.67}$	138-139 (2)	1.5053	840, 1030, 1150, 1580, 1600, 3010	146-147	72
<b>3b</b>	$\text{C}_{18}\text{H}_{29}\text{NO}$	$\frac{78.08}{78.54}$	$\frac{10.23}{10.54}$	$\frac{5.34}{5.09}$	157-158 (2)	1.5062	840, 1040, 1110, 1570, 1600, 3020	*	70
<b>3c</b>	$\text{C}_{14}\text{H}_{19}\text{NO}$	$\frac{77.80}{77.42}$	$\frac{8.41}{8.75}$	$\frac{6.17}{6.45}$	140-141 (2)	1.5370	840, 1030, 1140, 1600, 3030	154-155	73
<b>3d</b>	$\text{C}_{15}\text{H}_{21}\text{NO}$	$\frac{77.49}{77.92}$	$\frac{9.34}{9.09}$	$\frac{5.84}{6.06}$	145-146 (1)	1.5360	840, 1030, 1040, 1580, 1600, 3010	186-187	76
<b>3e</b>	$\text{C}_{14}\text{H}_{19}\text{NO}_2$	$\frac{72.49}{72.10}$	$\frac{8.38}{8.15}$	$\frac{6.25}{6.01}$	163-164 (1)	* <sup>2</sup>	850, 1040, 1100, 1580, 1600, 3010	180-181	81

\* Does not form picrate.

\*<sup>2</sup> Honey-like substance.TABLE 3. <sup>1</sup>H NMR Spectra of Amines **3a-e** and <sup>13</sup>C NMR Spectra of Amines **3c-e**

Com- pound	Chemical shifts, $\delta$ , ppm ( $J$ , Hz)						
	$\text{NCH}_2$ (2H, s)	6- $\text{CH}_3$ (3H, s)	H-1 (2H)	H-3 (2H)	H-5 (1H)	H-7 (1H)	R
<b>3a</b>	3.39	2.33	4.97 (m)	4.93 (m)	6.87 (s)	6.90 (s)	0.86 (6H, t, $J = 7.4$ , 2 $\text{CH}_3$ ); 1.45 (4H, sext., $J = 7.4$ , 2 $\text{CH}_2\text{CH}_3$ ); 2.30 (4H, m, 2 $\text{NCH}_2$ )
<b>3b</b>	3.38	2.33	4.95 (m)	4.93 (m)	6.87 (s)	6.89 (s)	0.87 (6H, t, $J = 7.4$ , 2 $\text{CH}_3$ ); 1.21-1.45 (8H, m, 2 $\text{CH}_2\text{CH}_2\text{CH}_3$ ); 2.32 (4H, t, $J = 7.2$ , 2 $\text{NCH}_2$ )
<b>3c*</b>	3.46	2.33	4.97 (m)	4.93 (m)	6.87 (br. s)	6.92 (br. s)	1.47 (4H, m, 2 $\text{NCH}_2\text{CH}_2$ ); 2.42 (4H, m, 2 $\text{NCH}_2$ )
<b>3d*</b>	3.30	2.33	4.97 (m)	4.93 (m)	6.87 (s)	6.87 (s)	1.43 (2H, m, $\text{N}(\text{CH}_2)_2\text{CH}_2$ ); 1.54 (4H, br. q, $J = 5.4$ , 2 $\text{NCH}_2\text{CH}_2$ ); 2.31 (4H, br. t, $J = 5.4$ , 2 $\text{NCH}_2$ )
<b>3e*</b>	3.36	2.33	4.99 (t, $J = 2.2$ )	4.93 (t, $J = 2.2$ )	6.90 (s)	6.90 (s)	2.34 (4H, m, 2 $\text{NCH}_2$ ); 3.58 (4H, m, 2 $\text{OCH}_2$ )

\* <sup>13</sup>C NMR spectrum,  $\delta$ , ppm: 20.65 ( $\text{CH}_3$ ); 23.05 ( $\text{NCH}_2\text{CH}_2$ ); 53.42 ( $\text{NCH}_2\text{CH}_2$ ); 57.81 ( $\text{NCH}_2$ ); 71.80 and 72.25 ( $\text{C}_{(1)}$  and  $\text{C}_{(3)}$ ); 119.23 and 127.35 ( $\text{C}_{(5)}$  and  $\text{C}_{(7)}$ ); 132.62, 134.82, 135.84 and 139.01 (Ar).\*<sup>2</sup> <sup>13</sup>C NMR spectrum,  $\delta$ , ppm: 20.62 ( $\text{CH}_3$ ); 23.90 ( $\text{NCH}_2\text{CH}_2$ ); 25.46 ( $\text{N}(\text{CH}_2)_2\text{CH}_2$ ); 53.89 ( $\text{NCH}_2\text{CH}_2$ ); 61.41 ( $\text{NCH}_2$ );71.91 and 72.16 ( $\text{C}_{(1)}$  and  $\text{C}_{(3)}$ ); 119.29 and 127.72 ( $\text{C}_{(5)}$  and  $\text{C}_{(7)}$ ); 132.04, 135.17, 135.75 and 139.13 (Ar).\*<sup>3</sup> <sup>13</sup>C NMR spectrum,  $\delta$ , ppm: 20.61 ( $\text{CH}_3$ ); 53.04 ( $\text{NCH}_2\text{CH}_2$ ); 61.03 ( $\text{NCH}_2$ ); 65.99 ( $\text{OCH}_2$ ); 71.88 and 72.21 ( $\text{C}_{(1)}$  and  $\text{C}_{(3)}$ );119.61 and 127.94 ( $\text{C}_{(5)}$  and  $\text{C}_{(7)}$ ); 131.04, 135.30, 135.93 and 139.30 (Ar).

with ether (3×100 ml) to separate amine **4a**. Yield 67%; bp 100-102°C (4 mm Hg),  $n_D^{20} = 1.4640$ , mp of picrate, 93-94°C (ethanol). IR spectrum (thin film),  $\nu$ ,  $\text{cm}^{-1}$ : 890, 1600, 2230, 3100.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm ( $J$ , Hz): 0.90 (6H, t,  $J = 7.3$ ,  $2\text{CH}_3\text{CH}_2$ ); 1.44 (4H, sext,  $J = 7.3$ ,  $2\text{CH}_3\text{CH}_2$ ); 1.87 (3H, dd,  $J_1 = 1.7$ ,  $J_2 = 7.0$ , =CCH<sub>3</sub>); 2.36 (4H, t,  $J = 7.3$ ,  $2\text{CH}_2\text{CH}_2\text{N}$ ); 3.41 (2H, s, CH<sub>2</sub>N); 5.14-5.17 (2H, br. s, =CH<sub>2</sub>). Found, %: N 7.51. C<sub>12</sub>H<sub>21</sub>N. Calculated, %: N 7.82.

**Preparation and Recyclization of Salts 2a-e. Dialkyl(6-methyl-1,3-dihydro-4-isobenzofuranmethyl)amines 3a-e (General Method).** A 2 N solution KOH (1.0-1.4 ml) (salt–base molar ratio 5:1) was added with shaking to a solution of salt **1a-e** (10-14 mmol) in water (2.5-3.5 ml). The reaction mixture was heated at 50-53°C for 5-10 min and then heating was terminated. The temperature of the reaction mixture spontaneously rose to 80-85°C and the mixture then gradually cooled to room temperature. The mixture was extracted with ether (2×35 ml). In each case, titration of the ethereal extract with 0.1 N sulfuric acid showed 12-15% amine **3a-e**. The picrates of these products did not give a depressed melting point when mixed with the picrate of amine **3a-e** obtained in the recyclization of salts **2a-e**. A twofold molar excess (relative to salt **1a-e**) of KOH dissolved in water (2 ml) was added to the reaction mixture after extraction with ether and the mixture was maintained at 85-90°C for 2.0-2.5 h. After cooling, the reaction mixture was extracted with ether (3×40 ml). The extract was washed with water and dried over anhydrous MgSO<sub>4</sub>. Then, ether was evaporated and amine **3a-e** was separated from the residue by vacuum distillation.

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