

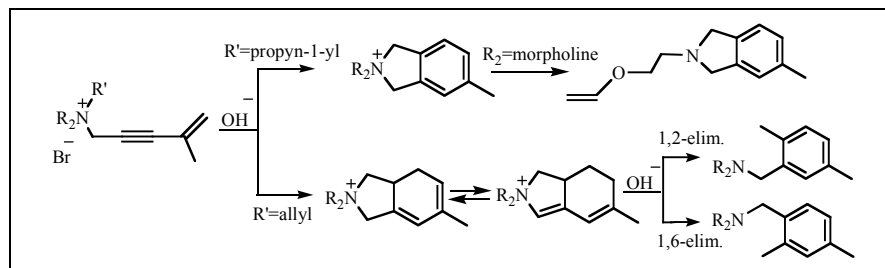
Cyclization of Dialkylpropyn-1-yl(allyl)(3-isopropenylpropyn-2-yl)ammonium Bromides and Water-Base Cleavage of 2,2-Dialkyl-5-methyl-2,6,7,7a-tetrahydro-1H-isoindolium and 2,2-Dialkyl-5-methylisoindolinium Bromides

Emma H. Chukhajian^{a*}, Martiros K. Nalbandyan^a, Hasmik R. Gevorkyan^a, Eliza H. Chukhajian^a, Henrik A. Panosyan^b, Armen G. Ayvazyan^b and Rafael A. Tamazyan^b

^a Institute of Organic Chemistry of National Academy of Sciences of the Republic of Armenia, Yerevan 375091, hasulik4@mail.ru

^b Molecule Structure Research Center of National Academy of Sciences of the Republic of Armenia, Yerevan 375014, henry@msrc.am

Received March 15, 2007



Dialkylpropyn-1-yl(or allyl)(3-isopropenylpropyn-2-yl)ammonium bromides under base-catalyzed condition instantly undergo intramolecular cyclization. The cyclization of dialkylpropyn-1-yl(3-isopropenylpropyn-2-yl)ammonium bromides leads to the formation of 2,2-dialkyl-5-methylisoindolinium salts. In case of allyl analogs, instead of the expected 2,2-dialkyl-6-methyl-3a,4-dihydroisoindolinium salts their isomeric forms – 2,2-dialkyl-5-methyl-2,6,7,7a-tetrahydro-1H-isoindolium bromides are obtained. In alkaline medium they are transform into the dihydroisoindolinium salts, the cleavage of which in two directions - 1,2 and 1,6 leads to the mixture of isomeric dialkyl-1,4-dimethyl- and 2,4-dimethylbenzylamines.

Study of the behavior of 2,2-dialkyl-5-methylisoindolinium salts under conditions of water-base cleavage showed, that only spiro[5-methylisoindolyn]morpholinium bromide undergoes 1,2-elimination, forming 5-methylisoindoline 2-vinyl ethyl ester.

J. Heterocyclic Chem., **45**, 687 (2008).

INTRODUCTION

Among practically important nitrogen-containing heterocycles, there is little data about isoindolinium and dihydroisoindolinium salts and their condensed analogs. This lack of data can be explained by the absence of available methods of synthesis of these salts.

The base-catalyzed intramolecular cyclization of ammonium salts, containing β,γ -unsaturated groups with enyne fragments of various types, first was discovered by A.T. Babayan, E.O. Chukhajian and other authors [1]. It includes enormous possibilities for obtaining bioactive isoindolinium, dihydroisoindolinium salts as well as their condensed analogs [2,3].

There are few works in literature dedicated to base-catalyzed intramolecular cyclization of compounds containing enyne fragments [4-9].

Since the base-catalyzed intramolecular cyclization of unsaturated ammonium salts leads to the new bioactive derivatives of isoindolinium salts, the expansion and development of investigations in this field are of great interest.

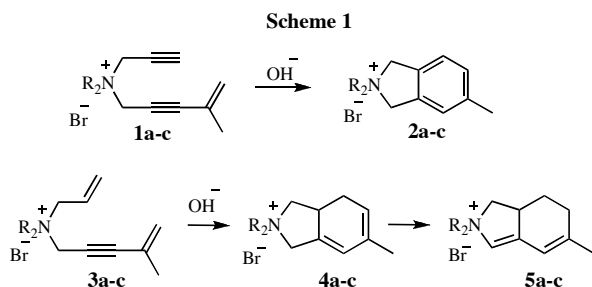
RESULTS AND DISCUSSION

Continuing the investigations, of the cyclization involved dialkylpropyn-1-yl(3-isopropenylpropyn-2-yl) (**1a-c**) and dialkylallyl(3-isopropenylpropyn-2-yl)ammonium (**3a-c**) bromides. Salts **1a-c** and **3a-c** were synthesized by alkylation of dialkyl(3-isopropenylpropyn-2-yl)amines, which have been prepared by the Mannich reaction [10,11]. Synthesis of (3-isopropenylpropyn-2-yl)pyrrolidine is described for the first time (see experimental section).

In case of success an accessible method for obtaining new derivatives of potentially bioactive isoindolinium and dihydroisoindolinium salts could be worked out. Apart from the preparative value these investigations include possibilities of revealing the influence of the methyl group in the enyne fragment in 4-th position on the cyclization process.

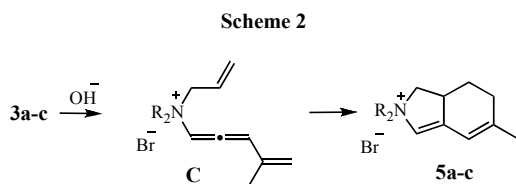
It was shown that salts **1a-c** and **3a-c** under base-catalyzed condition instantly undergo intramolecular cyclization even in molar ratio salt/alkali 13/1 by self-heating. In case of salts **1a-c** 2,2-tetramethylene- (**2a**),

2,2-pentamethylene-5-methylisindolinium (**2b**) and spiro[5-methylisindoline]morpholinium (**2c**) bromides are obtained in 83-85% yields. First discovered by us that in case of cyclization of allylic analogs **3a-c**, instead of the expected 2,2-dialkyl-6-methyl-3*a*,4-dihydroisindolinium bromides (**4a-c**) their isomeric forms – 2,2-tetramethylene- (**5a**), 2,2-pentamethylene-5-methyl-2,6,7,7*a*-tetrahydro-1*H*-isindolinium (**5b**) and spiro[5-methyl-2,6,7,7*a*-tetrahydro-1*H*-isindol]morpholinium (**5c**) bromides, are obtained in 85-87% yields (Scheme 1).



1a-5a; $R_2 = (-CH_2)_4$; **1b-5b**; $R_2 = (-CH_2)_5$; **1c-5c**; $R_2 = (CH_2)_2O(CH_2)_2$

It is supposed, that the formation of bromides **5a-c** includes the steps of salts **3a-c** prototropic isomerization into the salts with α -allenic grouping (**C**) and their cyclization (Scheme 2).

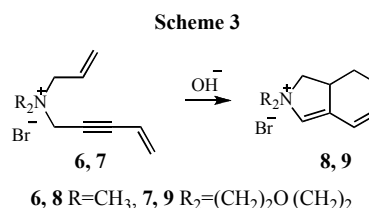


However, the above-mentioned assumption is incredible, because previously we showed, that during cyclization of ammonium salts, which contain β,γ -unsaturated groups along with enyne fragment of various types, the latter immediately takes part in the cycloaddition as a π^4 -fragment [12,13]. Salts **4a-c** (in its formation 3-alkenylpropyn-2-yl group is immediately involved in cyclization as a diene fragment) are more unstable compounds and in basic medium they are isomerized into salts **5a-c**.

Hybrid DFT (Density Functional Theory) calculations by B3LYP/6-31G(2d, p) method show that energy of the salts **4a-c** is 5 kcal/mol higher than that of salts **5a-c**. Evidently salts **4a-c** are really unstable compounds.

It was shown earlier, that by cyclization of dimethylallyl(3-vinylpropyn-2-yl)ammonium (**6**) and allyl(3-vinylpropyn-2-yl)morpholinium (**7**) bromides 2,2-dialkyl-3*a*,4-dihydroisindolinium salts were obtained [14,15]. It is necessary to note that on the 1H - and ^{13}C nmr spectral investigations basis, made on two cyclic salts examples, it

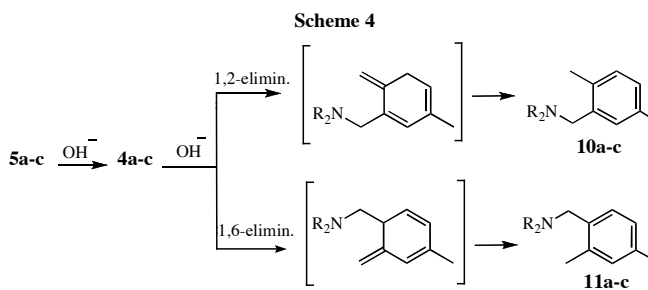
was established that in these cases also instead of the expected 2,2-dialkyl-3*a*,4-dihydroisindolinium salts their isomeric forms – 2,2-dimethyl-2,6,7,7*a*-tetrahydro-1*H*-isindolinium (**8**) and 2,2-spiro[2,6,7,7*a*-tetrahydro-1*H*-isindol]morpholinium bromides (**9**) are obtained as final products (Scheme 3).



The nmr spectral data of salts **8** and **9** are adduced in the experimental section. The structure of salt **9** also was determined by an X-ray diffraction method.

Based on the results of **5a-c** salts water-base cleavage it is assumed that in alkaline medium they are transform into the salts **4a-c** and the cleavage of salts **4a-c** in two directions – 1,2 and 1,6 leads to the mixture of isomeric dialkyl-1,4-dimethyl- (**10a-c**) and 2,4-dimethylbenzylamines (**11a-c**) in 66-69 % total yields (Scheme 4).

According to 1H nmr and GLC data the amount of isomeric amines in the mixture is almost equal.



10a,11a; $R_2 = (-CH_2)_4$; **10b,11b**; $R_2 = (-CH_2)_5$; **10c,11c**; $R_2 = (CH_2)_2O(CH_2)_2$

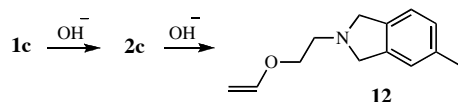
It is necessary to note that similar results are also obtained by cyclization of salts **3a-c** and direct water-base cleavage of their cyclic salts **5a-c**.

It was shown earlier that water-base cleavage of cyclic products, obtained by base catalyzed cyclization of dimethylallyl(3-isopropenylpropyn-2-yl)ammonium bromide, leads to the isomeric amines mixtures, in which the 1,2-elimination product comprises 89 % [16].

Comparing our data with those of literature it is possible to state that the voluminous substitutes, at the nitrogen atom, favorably affect the elimination process, proceeding in two directions – 1,2 and 1,6.

Study of the behavior of salts **2a-c** under conditions of water-base cleavage showed, that only salt **2c** undergoes 1,2-elimination, forming 5-methylisindoline 2-vinyl ethyl ester (**12**) in 62% yield (Scheme 5).

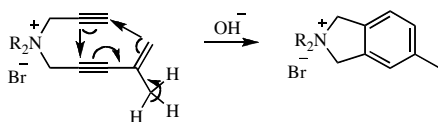
Scheme 5



Proceeding from the fact that it was impossible to obtain the salt **2c** in a crystalline form, we realized its immediate water-base cleavage after cyclization of propyn-1-yl(3-isopropenylpropyn-2-yl)morpholinium bromide without isolation of the cyclic product (**2c**).

According to several examples we confirmed that during base catalyzed intramolecular cyclization the base isn't consumed and in case of its absence no cyclization takes place. It means that the base is a momentum for the replacement of electrons with six-membered cyclic mechanism, clockwise or counterclockwise. The fact of salts **1a-c**, **3a-c** cyclization in milder conditions (molar ratio: salt/base=13/1) compared with the 3-vinylpropyn-2-yl analogs [14,15] (molar ratio: salt/base=10/1), allows to say that the methyl group available in the 4-th position of the enyne fragment increases the nucleophilicity of the enyne by its inductive and hyperconjugative effects. And so facilitates the nucleophile addition of 3-isopropenylpropyn-2-yl group to the propyn-2-yl or allylic group, including the six-membered cyclic mechanism electron replacement counter-clockwise (Scheme 6).

Scheme 6



These data are in accord with our investigations, dedicated to the mechanism of base-catalyzed intramolecular cyclization of unsaturated ammonium salts [12,13].

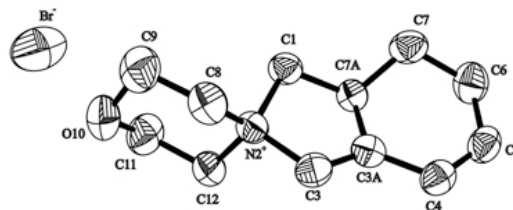
EXPERIMENTAL

The IR spectra were recorded on an IR-20 spectrometer. Samples were prepared as potassium bromide pellets or in Vaseline oil. The UV spectra were recorded on a Specord UV-vis spectrometer in ethanol. The NMR spectra were carried out on a "Varian Mercury-300" spectrometer at 300.08 MHz ¹H and 75.46 MHz for ¹³C at temperature of 303 K using TMS as an internal standard. For confirming the structures of salts **5a-c**, **8** and **9** as well as for assignment the signals in ¹H and ¹³C NMR spectra, methods of double resonance, DEPT and two-dimensional correlation COSY, NOESY, HMQC were used. Purity of salts was established by the TLC method on Silufol UV-254 in the system of 1-butanol/ethanol/water/acetic acid=10/2/1/5. Development was realized by iodine vapors. The purity of amines was established by the GLC method on the chromatograph LXM-8MD, column 1.5mx4mm, filled with

Inerton AW-HMDS, imbrued with 10% Carbovax-20M, gas-bearer - helium 40 mL/min. at the temperature 220°. Composition of the obtained compounds was consistent with the results of elemental analysis.

To determine the structure of the salt **9** X-ray diffraction structural investigation was carried out. The crystal of the size 0.2x0.24x0.28 mm was selected for diffraction measurements carried out on CAD4 "Enraf-Nonius" diffractometer. The compound has been crystallized in unusual for organic compounds high symmetric hexagonal space group P6₁ (N169). The set of 25 reflections with θ -angles in the range [14-15°] degrees was used to refine the lattice constants. The integral intensities of 14452 reflections were measured in full reciprocal sphere up to $\theta_{\text{max}}=30$ degree. The number of unique reflections was 3215 ($R_{\text{int}}=0.08$) from which the number of observed reflections was 1834 with criteria $I>2\sigma(I)$.

The initial structure model was defined by direct method using the package of crystallographic programs SHELXTL [17]. The hydrogen positions were determined from difference Fourier electron density maps. In final refinement the positional parameters of all atoms and anisotropic thermal parameters for nonhydrogen atoms were refined together giving final R value 0.053 for 1834 unique observed reflections. The crystal structure is constructed from C₁₂H₁₈ON⁺Br⁻ molecule and H₂O solvent water molecule, which is connected to Br⁻ ion by hydrogen bonding. The positional parameters of nonhydrogen atoms are given in the table 1. The interatomic distances are in agreement with their statistical values and are given in the table 2. The perspective view of the molecule with our numbering of atoms is depicted on the Figure 1. All necessary information on structural data may be obtained from authors.

Figure 1. The molecular structure of the salt **9**.

Spectra of the above-mentioned compounds accord well with suggested structures.

The initial dialkyl(3-isopropenylpropyn-2-yl)amines have been synthesized by the Mannich reaction [10,11].

(3-Isopropenylpropyn-2-yl)pyrrolidine (13). Isopropenylacetilene (33.5 g, 500 mmole), paraform (15.62 g, 520 mmole), pyrrolidine (28.4 g, 400 mmole), and 0.2 g of iron chloride and 150 mL of dioxane were placed in a metallic vessel. The reaction mixture was heated at 90-92 °C during 70 h and then the reaction mixture was acidified by hydrochloric acid. The

solvent was removed by distillation under low pressure. By alkalization of the hydrochloride and further extraction by ether (3x70 mL) amine **13** was isolated. The ethereal extract was washed with water and dried over magnesium sulfate. After

Table 1
Final Coordinates and Equivalent Isotropic Displacement,
Parameters of the non-Hydrogen atoms for the salt **9**.

Atom	x	y	z	U(eq) [Å ²]
O10	0.9389(3)	0.7200(2)	0.07500(11)	0.0687(8)
N2	0.9180(2)	0.4616(2)	0.13885(10)	0.0430(7)
C1	1.0400(3)	0.5143(3)	0.18601(13)	0.0454(9)
C3	0.8344(3)	0.2893(3)	0.14502(15)	0.0527(9)
C3A	0.9098(3)	0.2419(3)	0.17686(12)	0.0427(9)
C4	0.8694(3)	0.0860(3)	0.19378(14)	0.0488(9)
C5	0.9550(3)	0.0665(3)	0.23295(15)	0.0530(10)
C6	1.0887(4)	0.1948(4)	0.26280(16)	0.0614(13)
C7	1.0941(4)	0.3487(4)	0.25772(15)	0.0564(10)
C7A	1.0623(3)	0.3756(3)	0.19699(13)	0.0419(8)
C8	0.8085(3)	0.5230(4)	0.14664(17)	0.0545(10)
C9	0.8841(4)	0.6924(4)	0.13225(17)	0.0686(13)
C11	1.0538(4)	0.6764(4)	0.06833(17)	0.0646(11)
C12	0.9915(4)	0.5069(4)	0.08017(13)	0.0551(10)
O1W	0.4800(3)	0.4752(4)	0.26221(16)	0.1064(11)
Br	0.47692(4)	0.68352(4)	0.14811(2)	0.0684(1)

U(eq) = 1/3 of the trace of the orthogonalized U Tensor

Table 2
Bond Distances for the salt **9**.

Atom pair	distance[Å]	Atom pair	distance[Å]
O10-C9	1.418(5)	C1-H1A	0.89(3)
O10-C11	1.416(5)	C1-H1B	1.00(2)
O1W-H1WA	0.94(3)	C3-H3	0.98(3)
O1W-H1WB	1.03(8)	C4-H4	0.89(3)
N2-C1	1.523(4)	C5-H5	0.95(3)
N2-C12	1.512(4)	C6-H6B	0.98(4)
N2-C8	1.499(4)	C6-H6A	0.98(3)
N2-C3	1.488(3)	C7-H7A	1.06(3)
C1-C7A	1.521(4)	C7-H7B	0.87(3)
C3-C3A	1.299(5)	C7A-H7AA	1.08(3)
C3A-C4	1.446(4)	C8-H8A	0.94(4)
C3A-C7A	1.505(4)	C8-H8B	0.93(3)
C4-C5	1.327(5)	C9-H9B	0.92(3)
C5-C6	1.476(5)	C9-H9A	0.90(4)
C6-C7	1.506(5)	C11-H11A	1.02(3)
C7-C7A	1.506(5)	C11-H11B	0.93(4)
C8-C9	1.497(5)	C12-H12B	1.10(4)
C11-C12	1.500(5)	C12-H12A	0.86(3)

removing of the ether amine **13** (45.89 g, 308 mmole, 77%) was obtained by vacuum distillation, bp 63° (2 mm Hg), n_D^{20} 1.4910, mp of picrate 77° (EtOH). ir, ν , cm⁻¹: 890, 1610, 2240. ¹H nmr (DMSO -d₆/CCl₄ 1/3), δ , ppm: 1.75 (m, 4H, CH₂ pyrrolidine), 1.86 (dd, 3H, $J_1=1.6$ Hz; $J_2=1.2$ Hz, CH₃), 2.53 (m, 4H, NCH₂ pyrrolidine), 3.43 (s, 2H, NCH₂), 5.15 (kvn, 1H, $J=1.6$, =CH₂) and 5.17 (br, 1H, =CH₂). *Anal.* Calcd for C₁₀H₁₅N: C, 80.48; H, 10.13; N, 9.39. Found: C, 79.95; H, 10.38; N, 9.68

General procedure for the synthesis of salts **1a-c and **3a-c**.**
To a solution of (3-isopropenylpropyn-2-yl)pyrrolidine (**13**), -piperidine and -morpholine [11] (16 mmole) in 15 mL of absolute ether and 15 mL of acetonitrile a two-fold molar quantity of propyn-2-yl or allyl bromides were added. After two

days the salts **1a-c** and **3a-c** were isolated by filtration and washed with absolute ether (2 x 25 mL).

Propyn-1-yl(3-isopropenylpropyn-2-yl)pyrrolidinium bromide (1a). Salt **1a** (4.06 g, 15.52 mmole, 97%), mp 114°. uv, λ_{max} , nm: 225. ir, ν , cm⁻¹: 880, 1600, 2110, 2240. ¹H nmr (DMSO-d₆/CCl₄ 1/3), δ , ppm: 1.96 (m, 3H, CH₃); 2.26 (m, 4H, NCH₂CH₂); 3.86 (t, 4H, $J=6.0$ Hz, NCH₂CH₂); 3.75 (t, 1H, $J=2.5$ Hz, CH); 4.69 (d, 2H, $J=2.6$ Hz, NCH₂); 4.77 (s, 2H, NCH₂); 5.40 and 5.50 (m, 1H, =CH₂). ¹³C nmr (DMSO-d₆/CCl₄ 1/3), δ , ppm: 19.10 (NCH₂CH₂); 22.33 (CH₃); 49.39 (NCH₂); 50.24 (NCH₂); 57.26 (NCH₂CH₂); 70.85 (=C propin-1-yl); 75.16 (=C); 82.77 (=CH); 91.82 (=CC(CH₃)CH₂); 124.37 (=CH₂); 124.48 (=C). *Anal.* Calcd for C₁₃H₁₈BrN: C, 58.21; H,

6.72; Br, 29.79; N, 5.22. Found: C, 58.59; H, 6.65; Br, 29.44; N, 5.44.

Propyn-1-yl(3-isopropenylpropyn-2-yl)piperidinium bromide (1b). Salt **1b** (4.33 g, 15.36 mmole, 96%) mp 102°. uv, λ_{\max} , nm: 220. ir, ν , cm^{-1} : 890, 1605, 2120, 2240. ^1H nmr (DMSO- d_6 /CCl $_4$ 1/3), δ , ppm: 1.72 (m, 2H, CH $_2$ piperidine); 1.96 (m, 4H, NCH $_2$ CH $_2$); 1.96 (m, 3H, CH $_3$); 3.75 (t, 4H, $J=6.0$ Hz, NCH $_2$ CH $_2$); 3.77 (t, 1H, $J=2.5$ Hz, CH); 4.69 (d, 2H, $J=2.6$ Hz, NCH $_2$); 4.77 (s, 2H, NCH $_2$); 5.42 and 5.51 (m, 1H, =CH $_2$). ^{13}C nmr (DMSO- d_6 /CCl $_4$ 1/3), δ , ppm: 19.10 (NCH $_2$ CH $_2$); 20.11 (CH $_2$ piperidine); 22.33 (CH $_3$); 49.39 (NCH $_2$); 50.24 (NCH $_2$); 57.26 (NCH $_2$ CH $_2$); 70.85 (=C propin-1-yl); 75.16 (=C); 82.77 (=CH); 91.82 (=CC(CH $_3$)CH $_2$); 124.37 (=CH $_2$); 124.48 (=C). *Anal.* Calcd for C $_{14}$ H $_{20}$ BrN: C, 59.57; H, 7.09; Br, 28.31; N, 4.96. Found: C, 59.86; H, 6.82; Br, 28.62; N, 4.66.

Propyn-1-yl(3-isopropenylpropyn-2-yl)morpholinium bromide (1c). Salt **1c** (4.40 g, 15.52 mmole 97%), mp 122°. uv, λ_{\max} , nm: 230. ir, ν , cm^{-1} : 870, 1610, 2130, 2230. ^1H nmr (DMSO- d_6 /CCl $_4$ 1/3), δ , ppm: 1.99 (m, 3H, CH $_3$); 3.78 (m, 4H, NCH $_2$ morpholine); 3.86 (t, 1H, $J=2.5$, CH); 4.07 (m, 4H, OCH $_2$); 4.89 (d, 2H, $J=2.5$ Hz, NCH $_2$); 4.96 (s, 2H, NCH $_2$); 5.43 and 5.53 (m 1H, =CH $_2$). ^{13}C nmr (DMSO- d_6 /CCl $_4$ 1/3), δ , ppm: 21.79 (CH $_3$); 49.34 (NCH $_2$); 50.37 (NCH $_2$); 55.38 (NCH $_2$ morpholine); 59.00 (OCH $_2$); 70.18 (=C propin-1-yl); 74.40 (=C); 82.64 (=CH); 91.84 (=CC(CH $_3$)CH $_2$); 114.71 (=C); 123.95 (=CH $_2$). *Anal.* Calcd for C $_{14}$ H $_{18}$ BrNO: C, 54.93; H, 6.34; Br, 28.12; N, 4.93. Found: C, 54.75; H, 6.22; Br, 28.34; N, 4.69.

Allyl(3-isopropenylpropyn-2-yl)pyrrolidine bromide (3a). Salt **3a** (4.19 g, 15.52 mmole, 97%), mp 104°. uv, λ_{\max} , nm: 225. ir, ν , cm^{-1} : 890, 910, 940, 1610, 1635, 2240. ^1H nmr (DMSO- d_6 /CCl $_4$ 1/3), δ , ppm: 1.95 (m, 4H, NCH $_2$ CH $_2$); 1.96 (m, 3H, CH $_3$); 3.66 (t, 4H, $J=5.8$ Hz, NCH $_2$ CH $_2$); 4.26 (d, 2H, $J=7.3$ Hz, NCH $_2$); 4.77 (s, 2H, NCH $_2$); 5.42 and 5.49 (m, 1H, =CH $_2$); 5.67 and 5.79 (dd, 1H, $J_1=10.0$ Hz, $J_2=1.7$ Hz and $J_1=16.8$ Hz, $J_2=1.7$ Hz CH $_2$); 6.11 (ddt, 1H, $J_1=16.8$ Hz, $J_2=10.0$ Hz, $J_3=7.3$ Hz CH); ^{13}C nmr (DMSO- d_6 /CCl $_4$ 1/3), δ , ppm: 21.60 (NCH $_2$ CH $_2$); 22.39 (CH $_3$); 49.32 (NCH $_2$); 59.74 (NCH $_2$ CH $_2$); 60.93 (NCH $_2$); 75.94 and 91.47 (=C); 124.09 (=CH $_2$); 124.54 (=C); 124.65 (=C allyl); 127.43 (=CH $_2$ allyl). *Anal.* Calcd for C $_{13}$ H $_{20}$ BrN: C, 57.78; H, 7.41; Br, 29.57; N, 5.18. Found: C, 57.50; H, 7.55; Br, 29.25; N, 5.36.

Physico-chemical characteristics of the salts **3b** and **3c** are in accordance with literature data [11].

General procedure for the cyclization of salts 1a-c and 3a-c. To a solution of salts **1a-c** (8.7 mmole) in 3 mL of water or salts **3a-c** (12 mmole) in 5 mL of water was added 0.35 or 0.46 mL of 2 *N* solution of potassium or sodium hydroxide (mole-ratio:salt/base=13/1). During 5-6 min the reaction mixture temperature rose from 25° to 80-85° by self-heating. After cooling, the reaction mixture was extracted by ether (2x30 mL) for removing the products of the side reaction. The reaction mixture was acidified by hydrobromic acid then the solvent was removed by distillation under low pressure. The cyclic salts were extracted by absolute ethanol. Then salts **2a**, **2b**, **5a** were isolated by absolute ethereal settlement from ethanol solution. Salts **5b** and **5c** were isolated from the reaction mixtures by filtration at room temperature. It was impossible to obtain the salt **2c** in a crystalline form.

2,2-Tetramethylene-5-methylisoindolinium bromide (2a). Salt **2a** (1.93 g, 7.22 mmole, 83%), mp 194°. uv, λ_{\max} , nm: 245. ir, ν , cm^{-1} : 820, 850, 1580, 1600, 3020, 3070. ^1H nmr (DMSO- d_6 /CCl $_4$ 1/3), δ , ppm: 2.27 (m, 4H, NCH $_2$ CH $_2$); 2.38 s (3H, CH $_3$);

3.82 m (4H, NCH $_2$ CH $_2$); 4.96 (s, 2H, NCH $_2$); 4.98 (s, 2H, NCH $_2$); 7.18 (d, 1H, $J=7.7$ Hz, H $_{Ar}$); 7.23 (br, 1H, H $_{Ar}$); 7.30 (d 1H, $J=7.7$ Hz, H $_{Ar}$). ^{13}C nmr (DMSO- d_6 /CCl $_4$ 1/3), δ , ppm: 20.87 (CH $_3$); 29.17 (NCH $_2$ CH $_2$); 62.91 (NCH $_2$ CH $_2$); 65.73 (NCH $_2$); 123.06 (=CH); 123.45 (=CH); 128.97 (=CH); 129.56 (=C); 133.62 (=C); 136.9 (=C). *Anal.* Calcd for C $_{13}$ H $_{18}$ BrN: C, 58.21; H, 6.72; Br, 29.79; N, 5.22. Found: C, 58.56; H, 6.52; Br, 29.49; N 5.47.

2,2-Pentamethylene-5-methylisoindolinium bromide (2b). Salt **2b** (2.1 g, 7.39 mmole, 85%), mp 192°. uv, λ_{\max} , nm: 248. ir, ν , cm^{-1} : 825, 1560, 1600, 3030, 3070. ^1H nmr (DMSO- d_6 /CCl $_4$ 1/3), δ , ppm: 1.77 (br.k, 2H, $J=5.8$ Hz CH $_2$ piperidine); 1.96 (brk, 4H, $J=5.8$ Hz, NCH $_2$ CH $_2$); 2.40 (s, 3H, CH $_3$); 3.75 (t, 4H, $J=5.8$ Hz, NCH $_2$ piperidine); 4.98 (br, 2H, NCH $_2$); 4.99 (br, 2H, NCH $_2$); 7.17 (d, 1H, $J=7.7$ Hz, H $_{Ar}$); 7.24 (br, 1H, H $_{Ar}$); 7.31 (d, 1H, $J=7.7$ Hz, H $_{Ar}$). ^{13}C nmr (DMCO- d_6 /CCl $_4$ 1/3), δ , ppm: 20.53 (CH $_2$ piperidine); 20.82 (NCH $_2$ CH $_2$); 59.29 (NCH $_2$ piperidine); 66.27 (NCH $_2$); 122.88 (=CH); 123.53 (=CH); 128.80 (=CH); 129.89 (=C); 133.01 (=C); 137.78 (=C). *Anal.* Calcd for C $_{14}$ H $_{20}$ BrN: C, 59.57; H, 7.09; Br, 28.31; N, 4.96. Found: C, 59.88; H, 6.92; Br, 28.65; N, 5.21.

2,2-Tetramethylene-5-methyl-2,6,7,7a-tetrahydro-1H-isoindolium bromide (5a). Salt **5a** (2.78 g, 10.32 mmole, 86%), mp 192°. ir, ν , cm^{-1} : 1600, 1640, 3080. ^1H nmr (DMSO- d_6 /CCl $_4$ 1/3), δ , ppm: 1.52 (qd, 1H, $J_1=12.3$ Hz, $J_2=5.3$ Hz, CHCH $_2$); 1.79 (s, 3H, CH $_3$); 2.13 (m, 1H, CHCH $_2$); 2.22 (m, 4H); 2.25 (m, 2H, =CCH $_2$); 3.31 (m, 1H, CH); 3.43 (t, 1H, $J=10.3$ Hz, NCH $_2$); 3.55 (dt, 1H, $J_1=11.0$ Hz, $J_2=8.2$ Hz); 3.76 (m, 1H); 3.89-4.00 (m, 2H); 4.36 (dd, 1H, $J_1=11.0$ Hz, $J_2=6.8$ Hz); 6.12 (br, 1H, =CH); 6.46 (br, 1H, NCH=). ^{13}C nmr (DMCO- d_6 /CCl $_4$ 1/3), δ , ppm: 21.33 (CH $_2$); 21.61 (CH $_2$); 23.43 (CH $_3$); 25.49 (CH $_2$); 29.85 (CH $_2$); 38.40 (CH); 63.32 (NCH $_2$); 64.67 (NCH $_2$); 66.92 (NCH $_2$); 113.63 (=CH); 124.11 (=CHN); 137.85 (=C); 147.19 (=C). *Anal.* Calcd for C $_{13}$ H $_{20}$ BrN: C, 57.78; H, 7.41; Br, 29.57; N, 5.18. Found: C, 57.43; H, 7.52; Br, 29.85; N, 5.39.

2,2-Pentamethylene-5-methyl-2,6,7,7a-tetrahydro-1H-isoindolium bromide (5b). Salt **5b** (2.98 g, 10.20 mmole, 85%), mp 237°. ir, ν , cm^{-1} : 1605, 1650 3070. ^1H nmr (DMSO- d_6 /CCl $_4$ 1/3), δ , ppm: 1.53 (qd, 1H, $J_1=12.2$ Hz, $J_2=5.3$ Hz, CHCH $_2$); 1.62-1.80 (m, 2H); 1.85-2.05 (m, 4H); 1.90 (s, 3H, CH $_3$); 2.14 (m, 1H, CHCH $_2$); 2.20 (m, 1H, =CCH $_2$); 2.33 (m, 1H, =CCH $_2$); 3.27 (m, 1H, CH); 3.34 (t, 1H, $J=10.5$ Hz, NCH $_2$); 3.58 (m, 2H); 3.64 (ddd, 1H, $J_1=12.3$ Hz, $J_2=6.4$ Hz, $J_3=3.8$ Hz); 3.77 (ddd, 1H, $J_1=12.3$ Hz, $J_2=9.0$ Hz, $J_3=3.8$ Hz); 4.46 (dd, 1H, $J_1=11.0$ Hz, $J_2=6.8$ Hz); 6.12 (br, 1H, =CH); 6.57 (br, 1H, NCH=). ^{13}C nmr (DMCO- d_6 /CCl $_4$ 1/3), δ , ppm: 20.10 (CH $_2$); 21.33 (CH $_2$); 20.60 (CH $_2$); 21.11 (CH $_2$); 23.44 (CH $_3$); 25.62 (CH $_2$); 29.84 (CH $_2$); 37.66 (CH); 60.09 (NCH $_2$); 62.42 (NCH $_2$); 65.36 (NCH $_2$); 113.67 (=CH); 124.70 (=CHN); 137.74 (=C); 147.41 (=C). *Anal.* Calcd for C $_{14}$ H $_{22}$ BrN: C, 59.15; H, 7.75; Br, 28.11; N, 4.93. Found: C, 58.80; H, 8.00; Br, 28.39; N, 4.54.

Spiro[5-methyl-2,6,7,7a-tetrahydro-1H-isoindol]morpholinium bromides (5c). Salt **5c** (2.98 g, (10.44 mmole 87%), mp 247°. ir, ν , cm^{-1} : 1600, 1640, 3080. ^1H nmr (DMSO- d_6 /CCl $_4$ 1/3), δ , ppm: 1.56 (qd, 1H, $J_1=12.4$ Hz, $J_2=5.4$ Hz, CHCH $_2$); 1.89 (s, 3H, CH $_3$); 2.14 (m, 1H, CHCH $_2$); 2.20 (m, 1H, =CCH $_2$); 2.34 (m, 1H, =CCH $_2$); 3.35 (m, 1H, CH); 3.54 (t, 1H, $J=10.5$ Hz, NCH $_2$); 3.57-3.77 (m 3H); 3.83-4.12 (m, 5H); 4.68 (dd, 1H, $J_1=11.2$ Hz, $J_2=7.1$ Hz); 6.13 (br, 1H, =CH); 6.72 (br, 1H, NCH=). ^{13}C nmr (DMCO- d_6 /CCl $_4$ 1/3), δ , ppm: 23.48 (CH $_3$); 25.47 (CH $_2$); 29.85 (CH $_2$); 37.66 (CH); 58.90 (NCH $_2$); 60.98 (NCH $_2$); 61.17 (OCH $_2$); 61.69 (OCH $_2$); 65.36 (NCH $_2$); 113.56

(=CH), 124.49 (=CHN), 138.34 (=C), 147.84 (=C). *Anal.* Calcd for $C_{13}H_{20}BrNO$: C, 54.55; H, 7.04; Br, 27.92; N, 4.89. Found: C, 54.25; H, 7.26; Br, 28.23; N, 4.65.

2,2-Dimethyl-2,6,7,7a-tetrahydro-1H-isoindolium bromide (8). Salt **8** was obtained in 87% yield, mp 162°. ir, ν , cm^{-1} : 1650, 3010. 1H nmr (DMSO- d_6 /CCl $_4$ 1/3), δ , ppm: 1.54 (m, 1H, CHCH $_2$), 2.12 (m, 1H, CHCH $_2$), 2.43 (m, 2H, CH $_2$), 3.38 (s, 3H, CH $_3$) and 3.49 (s, 3H, CH $_3$), 3.38-3.54 (m, 2H, CH and NCH $_2$), 4.39 (m, 1H, NCH $_2$), 6.25 (ddd, 1H, $J_1=9.8$ Hz; $J_2=4.8$ Hz; $J_3=3.0$ Hz, =CHCH $_2$), 6.35 (dt, 1H, $J_1=9.8$ Hz; $J_2=2.0$ Hz, =CH), 6.61 (br, 1H, =CHN). ^{13}C nmr (DMSO- d_6 /CCl $_4$ 1/3), δ , ppm: 24.63 (CH $_2$), 25.12 (CH $_2$), 38.61 (CH), 52.44 (CH $_3$), 53.54 (CH $_3$), 69.88 (NCH $_2$), 117.80 (=CH), 128.53 (=CHN), 135.73 (=C), 137.70 (=CHCH $_2$). *Anal.* Calcd for $C_{10}H_{16}BrN$: C, 52.19; H, 7.01; Br, 34.72; N, 6.09. Found: C, 52.45; H, 7.16; Br, 34.60; N, 6.40.

2,2-Spiro[2,6,7,7a-tetrahydro-1H-isoindol]morpholinium bromide (9). Salt **9** was obtained in 82% yield, mp 240°. uv, λ_{max} , nm: 235. 1H nmr (DMSO- d_6 /CCl $_4$ 1/3), δ , ppm: 1.56 and 2.10 (m, 1H, CHCH $_2$), 2.24-2.43 (m, 2H, CH $_2$), 3.35 (m, 1H, CH), 3.48 (t, 1H, $J=11.0$ Hz, NCH $_2$), 3.57 (m, 1H, NCH $_2$ morpholine), 3.63 (ddd, 1H, $J_1=12.5$ Hz; $J_2=5.0$ Hz; $J_3=2.8$ Hz, NCH $_2$), 3.76 (ddd, 1H, $J_1=12.5$ Hz; $J_2=8.2$ Hz; $J_3=3.3$ Hz, NCH $_2$), 3.86-4.08 (m, 4H, OCH $_2$), 4.55 (dd, 1H, $J_1=11.0$ Hz; $J_2=6.9$ Hz, NCH $_2$ morpholine), 6.31 (ddd, 1H, $J_1=9.9$ Hz; $J_2=4.5$ Hz; $J_3=2.4$ Hz, =CHCH $_2$), 6.36 (dd, 1H, $J_1=9.9$ Hz; $J_2=1.8$ Hz, =CH), 6.69 (br, 1H, =CHN). ^{13}C nmr (DMSO- d_6 /CCl $_4$ 1/3), δ , ppm: 24.68 (CH $_2$), 25.27 (CH $_2$), 37.81 (CH $_2$ CH), 58.93 and 60.90 (NCH $_2$ morpholine), 61.07 and 61.54 (OCH $_2$), 65.38 (NCH $_2$), 117.82 (=CH), 126.20 (=CHN), 137.61 (=C), 138.61 (=CHCH $_2$). *Anal.* Calcd for $C_{12}H_{18}BrNO$: C, 52.95; H, 6.67; Br, 29.36; N, 5.15; O, 5.88. Found: C, 52.65; H, 6.83; Br, 29.70; N, 5.14.

General Procedure for the salts 5a-c water-base cleavage reaction. To a solution of salts **5a-c** (8.2 mmole) in 4 mL of water was added a two-fold molar quantity of potassium or sodium hydroxide dissolved in 3-4 mL of water. The cleavage reaction process and further treatment are analogous to the above-mentioned. The mixtures of isomeric amines **10a-c**, **11a-c** were distilled.

1-(2,5-Dimethylbenzyl)pyrrolidine (10a) and 1-(2,4-dimethylbenzyl)pyrrolidine (11a) (1 g, 5.33 mmole, with general yield 65%), bp 88-89° (1-2 mm Hg), n_D^{20} 1.5275. ir, ν , cm^{-1} : 805, 825, 1580, 1600, 3030. 1H nmr (DMSO- d_6 /CCl $_4$ 1/3), δ , ppm: 1.73 (m, 4H, CH $_2$ pyrrolidine), 2.27 (s, 1.5H, CH $_3$), 2.28 (s, 3H, CH $_3$), 2.29 (s, 1.5H, CH $_3$), 2.43 (m, 4H, NCH $_2$ pyrrolidine), 3.47 (s, 2H, NCH $_2$), 6.85-7.04 (m, 3H, H $_{Ar}$). *Anal.* Calcd for $C_{13}H_{19}N$: C, 82.54; H, 10.05; N, 7.41. Found: C, 82.91; H, 9.82; N, 7.62.

1-(2,5-Dimethylbenzyl)piperidine (10b) and 1-(2,4-dimethylbenzyl)piperidine (11b) (1.11 g, 5.49 mmole, with general yield 67%), bp 110° (1-2 mm Hg), n_D^{20} 1.5220. ir, ν , cm^{-1} : 825, 870, 1500, 1600, 3070. 1H nmr (DMSO- d_6 /CCl $_4$ 1/3), δ , ppm: 1.43 (m, 2H, CH $_2$ piperidine), 1.52 (m, 4H, NCH $_2$ CH $_2$), 2.27 (s, 1.5H, CH $_3$), 2.28 (s, 3H, CH $_3$), 2.29 (s, 1.5H, CH $_3$), 2.32 (m, 4H, NCH $_2$ piperidine), 3.30 (s, 2H, NCH $_2$), 6.80-7.01 (m, 3H, H $_{Ar}$). *Anal.* Calcd for $C_{14}H_{21}N$: C, 82.76; H, 10.34; N, 6.90. Found: C, 82.38; H, 10.61; N, 7.11.

4-(2,5-Dimethylbenzyl)morpholine (10c) and 4-(2,4-dimethylbenzyl)morpholine (11c) (1.16 g, 5.66 mmole, with general yield 69%), bp 105° (1-2 mm Hg), n_D^{20} 1.5240. ir, ν , cm^{-1} : 805, 825, 870, 1500, 1560, 1600, 3020. 1H nmr (DMSO- d_6 /CCl $_4$ 1/3), δ , ppm: 2.27 (s, 1.5H, CH $_3$), 2.28 (s, 1.5H, CH $_3$), 2.30 (s, 1.5H, CH $_3$), 2.31 (s, 1.5H, CH $_3$), 2.36 (m, 4H, NCH $_2$

morpholine), 3.36 (s, 2H, NCH $_2$), 3.57 (m, 4H, OCH $_2$), 6.84-7.02 (m, 3H, H $_{Ar}$). *Anal.* Calcd for $C_{13}H_{19}NO$: C, 76.10; H, 9.27; N, 6.83. Found: C, 75.71; H, 9.51; N, 6.58.

The step cyclization of the salt 1c and immediate cleavage of cyclic product. 5-Methylisoindoline 2-vinyl ethyl ester (12). To a solution of salt **1c** (9 mmole) in 3.5 mL of water was added 0.35 mL of 2 N solution of potassium or sodium hydroxide (mole-ratio:salt/base=13/1). The reaction mixture temperature rose up to 80-85° by self-heating during 5-6 min. After cooling, the reaction mixture was extracted by ether (2×30 mL) in order to remove the side reaction products. Then a two-fold molar quantity of potassium hydroxide was added to the reaction mixture. The cleavage carried out with distillation. From time to time water was added to the reaction mixture through a dropping funnel. During water-base cleavage the reaction mixture temperature is maintained at 110-120°. For the process completion the reaction mixture temperature was raised up to 140-145° for several minutes in the end. Then the reaction mixture and distillate were extracted by ether (3×40 mL). The ethereal extracts were combined and washed by water and dried over magnesium sulfate. After removing ether, amine **12** was distilled. Compound **12** (0.85 g, 4.2 mmole 60%), bp 125° (2 mm Hg.), oil. ir, ν , cm^{-1} : 810, 870, 1600, 1660, 3020, 3070, 3130. 1H nmr (DMSO- d_6 /CCl $_4$ 1/3), δ , ppm: 2.32 (s, 3H, CH $_3$), 2.96 (t, 2H, $J=5.9$ Hz, NCH $_2$), 3.82 (t, 2H, $J=5.9$ Hz, OCH $_2$), 3.95 (dd, 1H, $J_1=6.8$ Hz, $J_2=2.0$ Hz, =CH $_2$), 4.15 (dd, 1H, $J_1=14.3$ Hz, $J_2=2.0$ Hz, =CH $_2$), 6.44 (dd, 1H, $J_1=14.3$ Hz, $J_2=6.8$ Hz, =CH), 6.90-6.95 (m, 2H) and 7.00 (d, 1H, $J=7.4$ Hz, H $_{Ar}$). *Anal.* Calcd for $C_{13}H_{17}NO$: C, 76.85; H, 8.43; N, 6.90. Found: C, 76.47; H, 8.28; N, 7.14.

REFERENCES AND NOTES

- [1] Chukhajian, E. H.; *Khim. Geterotsikl. Soedin.* **1993**, *4*, 433.
- [2] Chukhajian, E. H.; Chukhajian, E. H.; Gevorkyan, H. R.; Shakhmatuni, K. G.; Kinoyan, F. S.; Panosyan, H. A. *Khim. Geterotsikl. Soedin.* **2004**, 34.
- [3] Gevorkyan, H. R.; Chukhajian, E. H.; Chukhajian, E. H.; Panosyan, H. A. *Khim. Geterotsikl. Soedin.* **2004**, 212.
- [4] Iwai, I.; Hiraoka, T. *Chem. Pharm. Bull.* **1963**, *11*, 1556.
- [5] Iwai, I.; Ide, J. *Chem. Pharm. Bull.* **1964**, *12*, 1094.
- [6] Bartlett, A. J.; Laird, T.; Ollis, W. D. *J. Chem. Soc., Chem. Commun.* **1974**, 496.
- [7] Bartlett, A. J.; Laird, T.; Ollis, W. D. *J. Chem. Soc., Perkin Trans. I* **1975**, 1315.
- [8] Laird, T.; Ollis, W. D.; *J. Chem. Soc., Chem. Commun.* **1972**, 557.
- [9] Garratt, P. J.; Neoh, S. B. *J. Am. Chem. Soc.* **1975**, *97*, 3255.
- [10] Mannich, C. *Ber.* **1933**, *66*, 418.
- [11] Chukhajian, E. H.; Gevorkyan, H. R.; Nalbandyan, M. K. *Russ. J. Org. Chem.* **2006**, *42*, 1784.
- [12] Chukhajian, E. H.; Gevorkyan, H. R.; Chukhajian, E. H.; Kinoyan, F. S. *Russ. J. Org. Chem.*, **2005**, *41*, 369.
- [13] Chukhajian, E. H.; Nalbandyan, M. K.; Gevorkyan, H. R.; Kinoyan, F. S. *Chem. J. Arm.*, **2007**, *60*, 83.
- [14] Babayan, A. T.; Chukhajian, E. H.; Babayan, G.; Chukhajian, E. H.; Kinoyan, F. S. *Chem. J. Arm.* **1970**, *23*, 149; *Chem. Abstr.* **1970**, *73*, 25225x.
- [15] Chukhajian, E. H.; Gabrielyan, G.; Babayan, A. T. *Chem. J. Arm.* **1976**, *29*, 649.
- [16] Babayan, A. T.; Taqmazyan, K.; Babayan, G. *Chem. J. Arm.* **1966**, *19*, 685; *Chem. Abstr.* **1967**, *66*, 104532d.
- [17] Bruker AXS, Copyright 2000, SHELXTL version 6.10.