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Synthesis of Polynuclear Isoindolinium Salts and the Transformation of Hydroxymethylisoindolinium Derivatives

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Abstract

The review is devoted base-catalyzed intramolecular cyclization of ammonium salts containing β,γ-unsaturated groups alongside with various enyne fragments. This process results in the formation of polynuclear isoindolinium salts and in the transformation (recyclization) of those containing the hydroxymethyl group at the position 4 in the aromatic ring.

Key words: unsaturated ammonium salts, base-catalyzed intramolecular cyclization, recyclization, double cyclization and recyclization, condensed isoindolinium and dihydrofuran derivatives, 4-hydroxymethyl derivatives of isoindolinium, sequence of cyclization and dehydrochlorination stages

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INTRODUCTION

Searching for ways to synthesize nitrogen- and oxygen-containing heterocyclic compounds represents one of the important tasks of organic chemistry. Besides the undoubted theoretical interest, these compounds have practical value: they are parts of natural antibiotics, alkaloids, proteins, cardiac glycosides, and so on. Among the nitrogen heterocycles important for practice there are compounds belonging to isoindolinium series and their condensed analogues especially poorly studied. To all appearance, the fact is connected with the deficiency of data concerning the methods for obtaining hard-to-synthesize compounds belonging to this series.

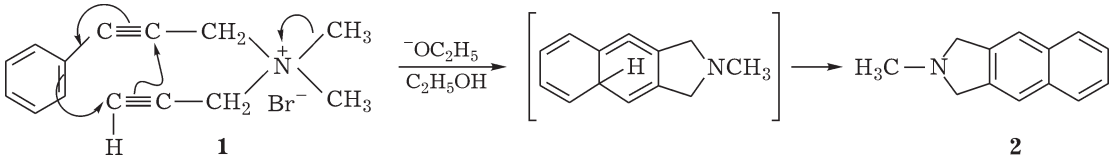
First discovered by A. T. Babayan, E. O. Chukhajan *et al.* [1], a base-catalyzed intramolecular cyclization of ammonium salts containing 1,2-unsaturated groups alongside with various enyne fragments represents a source of enormous potential for the synthesis of bioactive di-, tri- and polycyclic isoindolinium and dihydroisoindolinium salts, whereby depending on the structure of the starting unsaturated salts one could obtain either phenanthrene derivatives, or linearly annelated condensed nitrogen-containing heterocycles. Base-catalyzed intramolecular cyclization such as the diene synthesis of unsaturated ammonium salts represents a novel field in the organic and fine organic chemistry. Among isoindolinium salts there are representatives with a pronounced pharmacological activity protected by numerous author's certificates.

CYCLIZATION OF BIS(3-PHENYLPROPYN-2-YL)AMMONIUM BROMIDES

In 1963, the Japanese researchers [2] studied the behaviour of salt of **1** with respect to sodium ethoxide in absolute ethanol. As a reaction product, there was 2-methylbenzo[*f*]isoindolinium **2** obtained with a 22 % yield. For the formation of the mentioned amine the authors proposed a scheme involving synchronously running the reaction of nucleophilic substitution at the methyl group and cyclization [2] (Scheme 1).

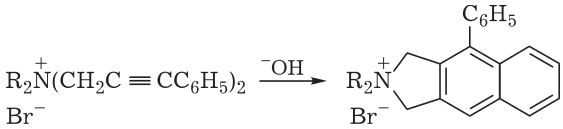
In the scheme proposed, we believe both the formation of six-membered ring, including allene bond system, and the nucleophilic substitution at the methyl group in the ammonium complex to be unlikely. Basing on our studies [3], we have assumed that, under the conditions of the experiment performed by the authors of [2] there should be also 2,2-dimethylbenzo[*f*]isoindolinium bromide formed. By repeating their experience, with changing only the extraction procedure for the reaction products [3], we revealed that the main product is really presented by 2,2-dimethylbenzo-[*f*]isoindolinium bromide that under the conditions of treating the reaction mixture was missed by Japanese researchers [2]. In a separate experiment, it was demonstrated that the amine **2** is formed by means of cleaving the cyclic salt.

In the same work, the authors reported the studies on the reaction of methyldimethyl-bis(3-phenylpropyn-2-yl)ammonium with sodium ethoxide in absolute ethanol, as well as with an aqueous sodium hydroxide solution. In the opinion of the authors, in the case of this salt there should also be 2-methyl-4-phenylbenzo[*f*]isoindolinium formed according to the above-mentioned scheme. However, contrary to the authors' expectations, the amine was not formed. On this basis, they concluded that the mentioned salt was not cyclised due to unfavourable steric factors. However, according to the results of [1, 3], we could expect the fact that there should occur the formation of the cyclization product of methyl 2,2-dimethyl-4-phenylbenzo[*f*]isoindolinium, rather than of the free amine. It was established that the dimethyl and other alkyl analogues undergo quantitative cyclization even in the presence of the traces of aqueous alkali, accompanied with



Scheme 1.

self-heating [4, 5] to form isoindolinium condensed analogues.



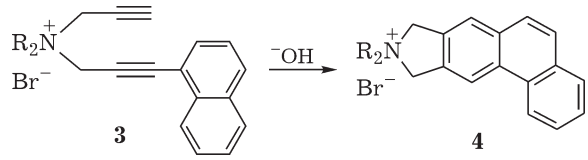
R = CH_3, C_2H_5; R_2 = $(CH_2)_4$, $(CH_2)_5$

Such salts are subjected to cyclization in the absence of a base under heating aqueous solutions thereof. After the publication of these studies [6, 7] it was reported that dimethylbis(3-phenylpropyn-2-yl)ammonium bromide can undergo intramolecular cyclization in the presence of catalytic quantities of aqueous sodium hydroxide solution, to result in the formation of corresponding cyclised product.

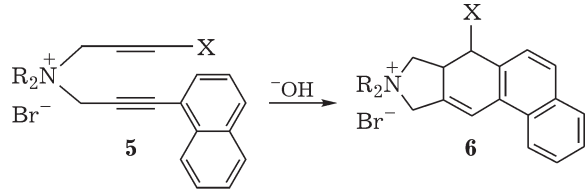
CYCLIZATION OF AMMONIUM SALTS CONTAINING 3-α-NAPHTHYLPROPYN-2-YL FRAGMENT ALONGSIDE WITH VARIOUS π^2 GROUPS

Cyclization of dialkylpropargyl(allyl or buten-2-yl)(3-α-naphthyl-2-propyn-2-yl)ammonium

It has been established that salts **3** in the presence of 0.2 M KOH solution per 1 mol of the salt taken are rapidly subjected to cycloaddition with self-heating to produce the derivatives of phenanthrene with quantitative yields [8, 9].



For the cyclization of allyl analogues **5** it is necessary for heating during 2 h at 90–92 °C [10]:

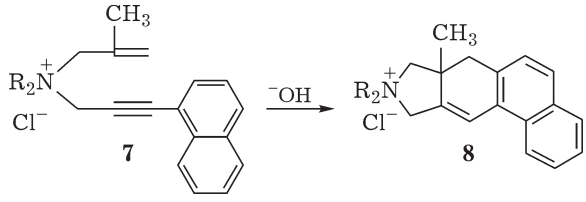


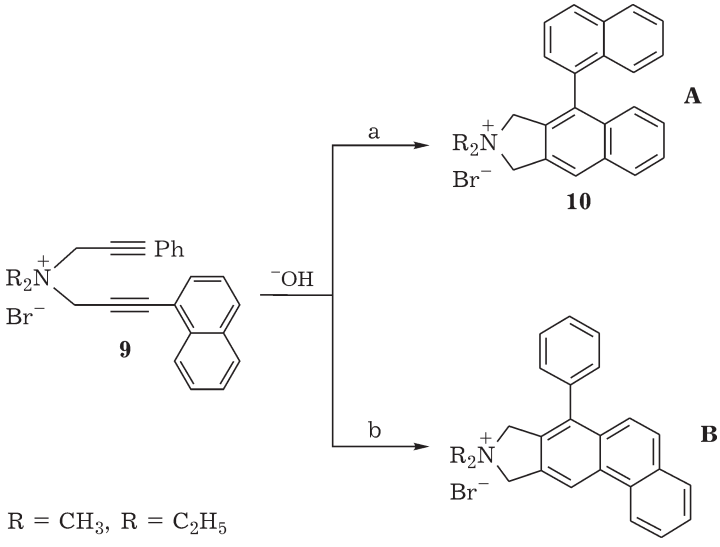
X = H, CH_3

Cyclic salts **6** are formed with almost quantitative yields.

Cyclization of dialkylmetallyl(3-α-naphthylpropyn-2-yl)ammonium chlorides

Continuing the studies it was established that, unlike the 3-phenylpropyn-2-yl analogues [11] those under the conditions of base catalysis are subjected to the only rearrangement-cleavage reaction, the salts **7** undergo mainly intramolecular cycloaddition (54–60 %) [12]. Alongside with the cyclization there occur rearrangement-cleavage reactions (8–10 %) and Stivenson rearrangement (6–10 %).





R = CH_3, R = C_2H_5

Scheme 2.

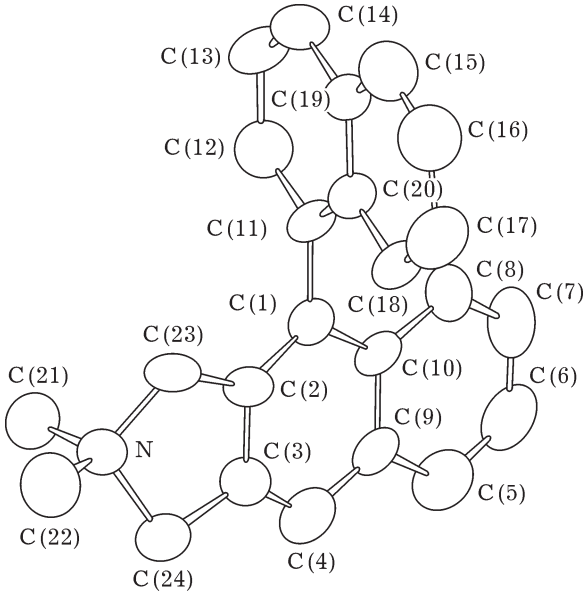


Fig. 1. Molecular structure of isomer **A** – 2,2-dimethyl-4-α-naphthylbenzo[*f*]isoindolinium bromide.

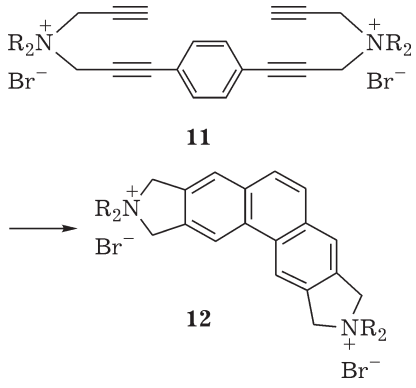
CYCLIZATION OF SALTS CONTAINING 3-PHENYLPROPYN-2-YL GROUP ALONGSIDE WITH 3-α-NAPHTHYLPROPYN-2-YL GROUP

The cyclization of salts **9** could occur in the directions **A** and **B**. There is a possibility that the process to occur in both directions simultaneously. According to the direction **A**, as the diene fragment there participates 3-phenylpropargyl group, whereas according to the direction **B** there is a participation of 3-α-naphthylpropargyl group observed (Scheme 2).

It was revealed that the salts **9** under the conditions of base catalysis undergo an ambiguous cycloaddition to form a mixture of isomeric products **A** and **B** with 70–72 % overall yield as the result of cyclization in both directions [13]. Isomeric cyclic products can be separated from each other by means of fractional crystallization from an alcoholic solution. In the case of the dimethyl analog there are 64 % of isomer **A** and 5 % of isomer **B** formed, whereas in the case of diethyl analog the formation of 73 % of isomer **A** and 7 % of isomer **B** is observed. The structure of isomer **A** was established by means of XRD structural analysis [13] (Fig. 1).

CYCLIZATION OF *p*-BIS[3-(DIALKYLPROPYN-2-YL-AMMONIUMPROPYN-1-YL)]BENZENE DIBROMIDE

It was established that salts **11** in the presence of 0.4 M solution of KOH per 1 mol of the salt taken are rapidly and almost quantitatively, with self-heating, subjected to the double cyclization, resulting in the formation of salts **12** [14].

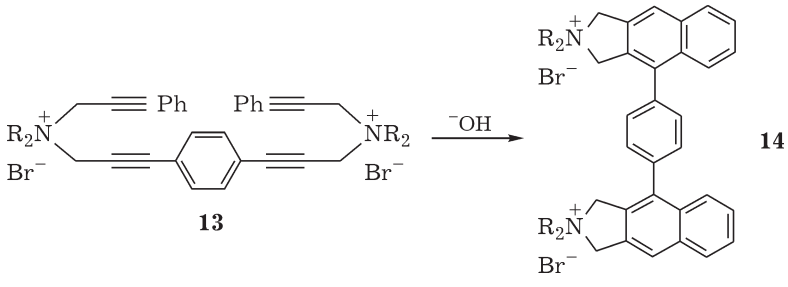


CYCLIZATION OF 3-PHENYLPROPYN-2-YL ANALOGUES

From the structure of salts **13** it follows that the cyclization can occur in two directions **A** or **B** (Scheme 3).

As a π^4 fragment, in the case of direction **A**, there can act 3-phenylpropyn-2-yl group, whereas in the case of direction **B** it is general group.

Using the XRD structural analysis it was revealed that the double cyclization of salts **13** results in a prevailing formation of *p*-phenylen-



Scheme 3.

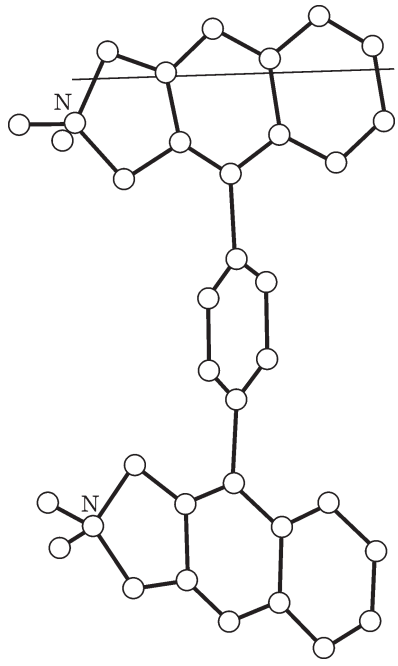


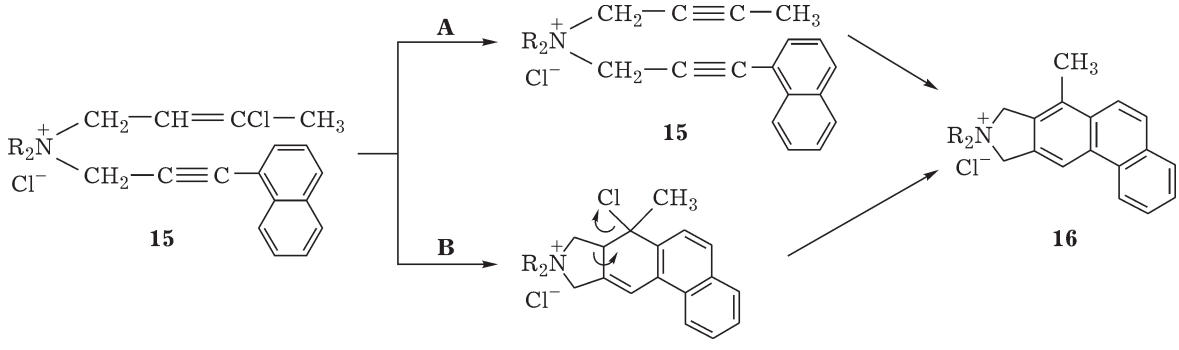
Fig. 2. Molecular structure of salt **14**.

bis-4,4′(2,2-dialkylbenzo[*f*]isoindolinium dibromides (14) (see Fig. 2) [15], *i. e.*, the 3-phenylpropyn-2-yl group acts in this case as a π^4 fragment.

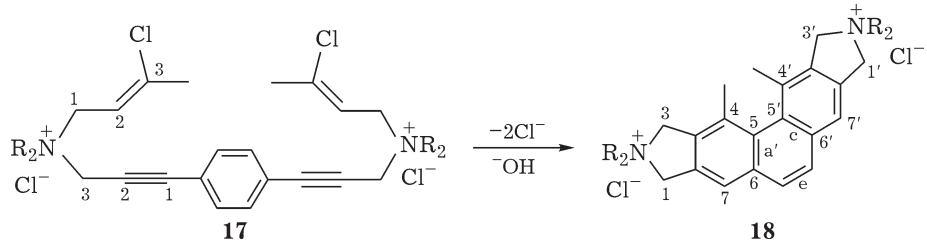
STUDYING THE BEHAVIOUR OF DIALKYL-3-CHLOROBUTEN-2-YL(3-α-NAPHTHYLPROPYN-2-YL)AMMONIUM CHLORIDES AND *p*-BIS{3-[*N*-(3-CHLOROBUTEN-2-YL)PYRROLIDINO(PIPERIDINO OR MORPHOLINO)]-PROPYN-1-YL}BENZENE DICHLORIDES

For the formation end products from the salts **15** and **17** there are two pathways those differ from each other in the sequence of cyclization and dehydrochlorination stages. According to the direction **A**, the starting salt is dehydrochlorinated first, and then the cyclization of an intermediate salt occurs, whereas in the case of pathway **B** the cyclization stage precedes the stage of dehydrochlorination. Basing on the final products **16** and **18** it is impossible to reveal the sequence of above mentioned reaction stages (Scheme 4).

Detailed studies we carried out in order to determine the sequence of these reaction stages demonstrated that the salts **15** in an aqueous alkaline medium undergo dehydrochlorination-cyclization (pathway **A**). The salts **17** are also subjected to dehydrochlorination-cyclization. From the salts **15** and **17**, isoindolinium salts **16** and **18** as end products are formed, containing the phenanthrene cycle [16–18] (Scheme 5).



Scheme 4.

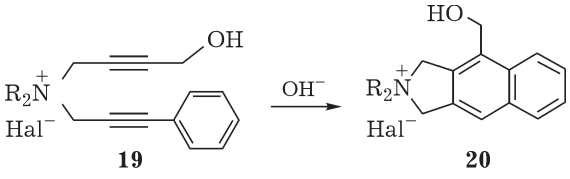


Scheme 5.

The derivatives of this cycle represent important naturally occurring compounds, such as cholesterol, ergosterol, plant and animal sterols.

CYCLIZATION OF DIALKYL(4-HYDROXYBUTYN-2-YL) (3-PHENYLPROPYN-2-YL)AMMONIUM HALIDES

Continuing the investigations in the field of the base-catalyzed intramolecular cyclization we established that in the mentioned reaction there can be successfully involved 4-hydroxybutyn-2-yl group as a π^2 fragment. It was demonstrated that the salts **19** in the presence of catalytic amounts of aqueous alkali undergo intramolecular cyclization to form 2,2-dialkyl-4-hydroxymethylbenzo[*f*]isoindolinium halides **20** with the yield of 75–80 % [19].



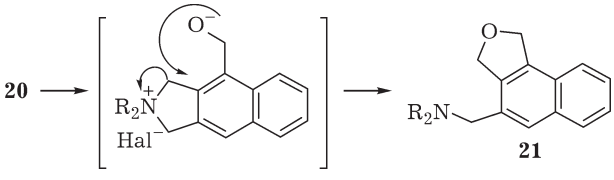
19 **20**

$Hal^- = Cl^-, Br^-$

The cyclization salts **19**, as to compare to propargyl analogues [8] occurs under much more severe conditions. So, the cyclization of propargyl analogues in the presence of 0.2 mol of aqueous alkali per 1 mol of the starting salt takes place at a room temperature with self-heating [3, 8], whereas the cyclization of the mentioned salts requires heating the reaction mixture up to 50–55 °C, whereupon the reaction proceeds with self-heating [19].

INTRAMOLECULAR RECYCLIZATION OF 2,2-DIALKYL-4-HYDROXYMETHYLBENZO[*f*]ISOINDOLINIUM HALIDES UNDER THE CONDITIONS OF AQUEOUS ALKALINE CLEAVAGE

In the course of studying the behaviour of salts **20** under the conditions of aqueous alkaline cleavage we revealed an intramolecular recyclization process involving the stages of disclosing the isoindolinium cycle under the influence of alkoxy anion formed in alkaline medium, with the formation of the dihydrofuran cycle [20].



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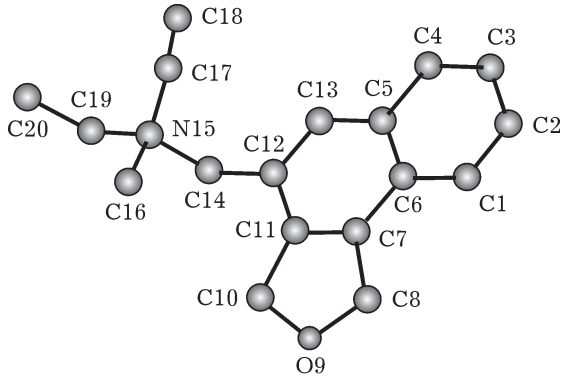
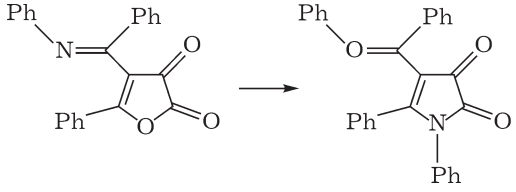


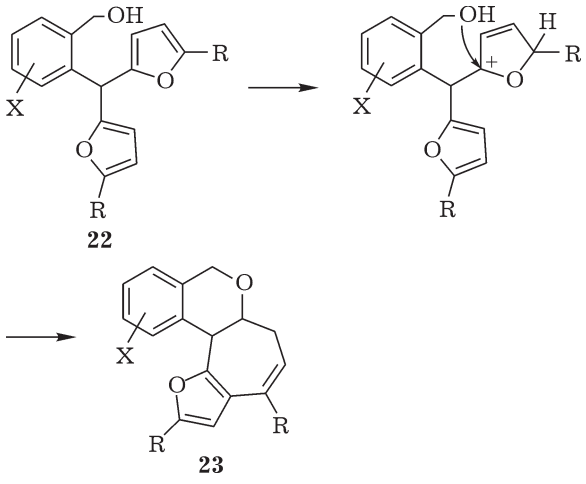
Fig. 3. Molecular structure of 1,3-dihydro-4-diethylaminomethylnaphtho[1,2-*c*]furan bromomethylate.

The process results in the formation of 1,3-dihydro-4-dialkylaminomethylnaphtho[1,2-*c*]furans **21** with the yield ranging within 75–85 % [20]. Amines **21** with the yield of 8–10 % are also formed in the course of the cyclization of starting salts **19** under the conditions of base catalysis. The structure of 1,3-dihydro-4-diethylaminomethylnaphtho[1.2-*c*]furan bromomethylate was established by means of XRD (Fig. 3) [20].

In the literature there is one example of a pure intramolecular recyclization known such as a thermal conversion of iminobenzylfurandiones into 4-acylpyrrole-2,3-diones [21].



After the publication of our studies devoted to the intramolecular recyclization of 2,2-dialkyl-4-hydroxymethylbenzo[*f*]isoindolinium [20] and 2,2-dialkyl-4-hydroxymethylisoindolinium salts [22, 23], the authors of [24] reported that 2-hydroxymethylaryldifurylmethanes under boiling in ethanol saturated with HCl, are subjected to recyclization at the expense of one of the furan rings to form the derivatives of isochromane. Under the acidic conditions, the hydroxymethyl group can act either as C-electrophile, or as O-nucleophile with respect to furan. According to the results of the reaction it as revealed that the hydroxymethyl group acts as an O-nucleophile [24].



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CYCLIZATION OF DIALKYL(4-HYDROXYBUTYN-2-YL) [3-(*p*-CHLOROPHENYL)PROPYN-2-YL]AMMONIUM CHLORIDES AND RECYCLIZATION OF PRODUCTS OBTAINED

It was demonstrated that salt **24**, just as the analogues investigated earlier such as (3-phenyl-, 3-vinyl-, 3-isopropenylpropyn-2-yl) [19, 22, 23] in the presence of an aqueous solution of 0.2 M KOH per 1 mol of the salt taken, can be after preheating up to 50–55 °C readily cyclised (exothermic reaction), to produce 2,2-dialkyl-4-hydroxymethyl-6-chlorobenzo[*f*]isoindolinium chlorides **25** with the yields of 60–65 % [25] (Scheme 6).

In this case, just as in the case of the cyclization of 3-phenyl-, 3-alkenyl, 3-alkenyl(propyn-2-yl) analogues [19, 22, 23, 26] there are also recyclization products of 1,3-dihydro-4-dialkylaminomethyl-8-chloronaphtho[1,2-*c*]furans **26** formed with the yield of 10–15 %.

The salts **25** under the conditions of aqueous alkaline cleavage quite smoothly undergo the recyclization as to compare to 4-hydroxymethylbenzo[*f*]isoindolinium and 4-hydroxymethylisoindolinium salts [17, 20, 22, 23, 26].

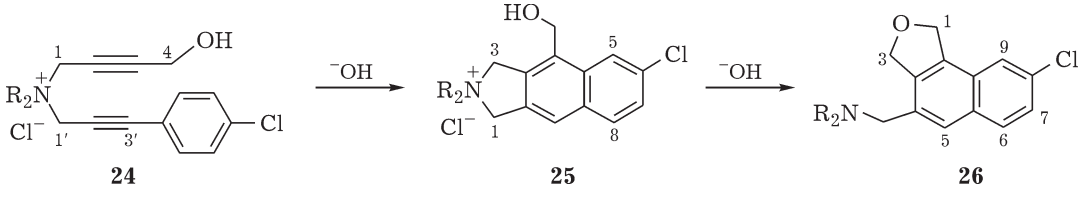
Amines **26** are formed with the yield of 62–68 %. In the course of sequential performing the cyclization and recyclization with no isolation of the cyclization products of compound **25**, ont can observe amines **26** to be formed with the total yield of 75–82 % [25].

CYCLIZATION OF DIALKYL(4-HYDROXYBUTYN-2-YL)-[3-(*p*-TOLYL)PROPYN-2-YL]AMMONIUM CHLORIDES AND RECYCLIZATION OF PRODUCTS OBTAINED

It was demonstrated that the cyclization of salts **27** under the conditions of base catalysis except for the morpholinium analogue, occurs under much more severe conditions (in the presence of an equimolar amount of aqueous alkali) [27] as compared to the 3-phenyl-3-*p*-chlorophenyl analogues thereof, in the case when the salt/base ratio amounted to 5 : 1 [19, 25] (Scheme 7).

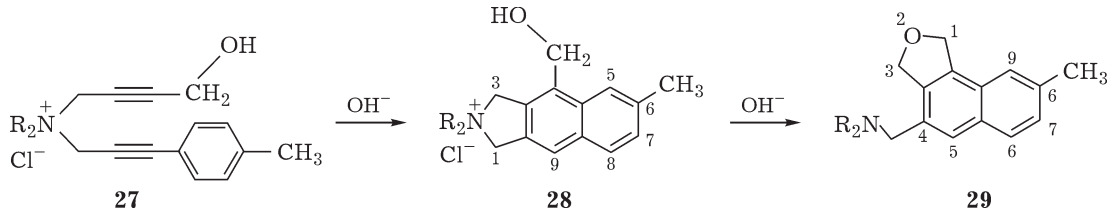
The cyclization of the morpholinium salt occurs with rapid self-heating even at a molar ratio salt/KOH = 5 : 1.

The recyclization salts **28** was carried out with no isolation them from the reaction mix-



24 **25** **26**

Scheme 6.



27 **28** **29**

R = CH_3, C_2H_5, C_3H_7; R_2 = $(CH_2)_4$, $(CH_2)_5$, (CH_2OCH_2)

Scheme 7.

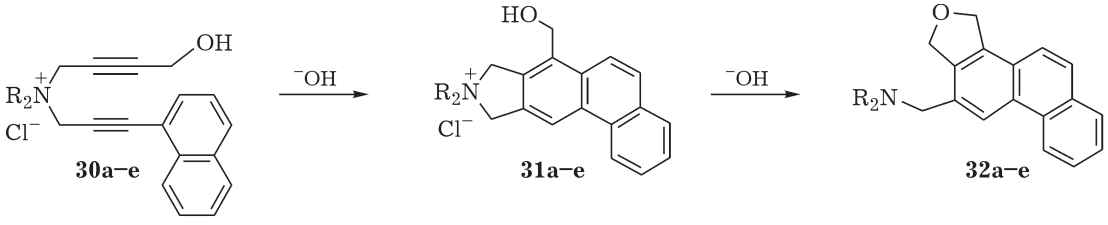
ture after the cyclization of the salts 27 [27]. Amines **29** were obtained with the total yield ranging within 62–70 %. Meanwhile, the dimethyl analog of the salt **29** can be formed only with the yield equal to 32 % because of gumming. The amines **29** with the yield of 8–15 % can be obtained also in the course of the cyclization of salts **27** under the conditions of base catalysis.

INFLUENCE OF THE NUMBER OF AROMATIC RINGS AND BULKY SUBSTITUENTS AT THE NITROGEN ATOM UPON INTRAMOLECULAR CYCLIZATION AND RECYCLIZATION

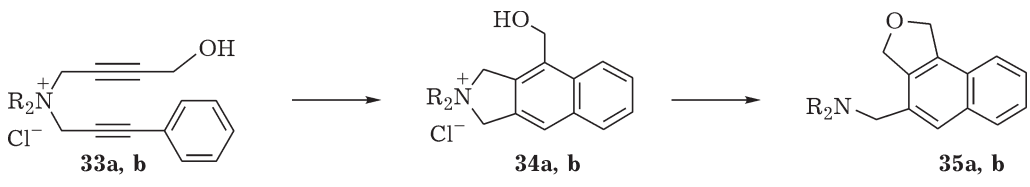
In order to reveal the impact of structural factors on the intramolecular cyclization and subsequent recyclization of isoindolinium derivatives formed we studied the behaviour of the chlorides of diethyl(4-hydroxy-2-butinyl)(3-α-naphthylpropyn-2-yl)ammonium **30a**, dipropyl(4-hydroxybutyn-2-yl)(3-α-naphthylpropyn-2-yl)ammonium **30b**, (4-hydroxybutyn-2-yl)(3-α-naphthylpropyn-2-yl)pyrrolidinium **30c**, (4-hydroxybutyn-2-yl)(3-α-naphthylpropyn-2-yl)piperidinium **30d**, (4-hydroxybutyn-2-yl)(3-α-naphthylpropyn-2-yl)morpholinium **30e**, as well as 4-fluorophenyl(4-hydroxybutyn-2-yl)(3-phenylpropyn-2-yl)piperazinium **33a** and dicyclohexyl(4-hydroxybutyn-2-yl)(3-phenylpropyn-2-yl)ammonium **33b** under the conditions of the base catalysis.

It was demonstrated that the cyclization of the mentioned salts in comparison to the propargyl analogues thereof [8, 9] proceeds under much more severe conditions. So, the cyclization of dialkylpropargyl(3-α-naphthylpropyn-2-yl) or (3-phenylpropyn-2-yl)ammonium salts takes place at a room temperature with rapid self-heating, whereas the salts **30a–e**, **33a, b** undergo cyclization in the presence of an equimolar amount of KOH in the course of heating the reaction mixture during 5–10 min to 50–55 °C, whereupon the temperature of the reaction mixture exhibits an increase up to 78–80 °C *via* self-heating [28, 29] (Scheme 8).

The requirement for more severe conditions for salts **30a–e**, **33a, b**, first of all is, to all appearance, connected with the fact that the naphthyl fragment is much more bulky as compared to the phenyl fragment, as well as bulky substituents at the nitrogen atom (steric factor), which is unfavourable for this reaction. There could be also a negative role of a greater electron-donor ability of the naphthyl fragment, since the latter makes it difficult to realize the electron transfer according to a six-membered cyclic counterclockwise mechanism, which was just observed in the course of replacing the phenyl substituent by a more electron-donating tolyl substituent (electronic factor) [27]. Much more severe cyclization conditions for the salts under investigation, as in the



30a, 31a, 32a: R = C_2H_5; **30b, 31b, 32b**: R = C_3H_7; **30c, 31c, 32c**: R_2 = $(CH_2)_4$; **30d, 31d, 32d**: R_2 = $(CH_2)_5$; **30e, 31e, 32e**: R_2 = $(CH_2)_2O(CH_2)_2$



33a, 34a, 35a: R_2 = F–C6H4–N(CH2)4 **33b, 34b, 35b**: R = C6H11

Scheme 8.

case of the other 4-hydroxybutyn-2-yl analogues [19, 22, 23, 25] could be explained either by the presence of hydroxyl groups in the molecules of salt **30a–e** and **33a, b** (hindering the nucleophilic attack by diene fragment onto the carbon atom located at the third position of the dienophile), or by decreasing the concentration of alkali resulting from the formation of corresponding alcoholates those can again undergo the transformation into the initial state in aqueous solution.

There is a possibility of simultaneous influence of both factors upon the course of the process. For the case of the cyclization of salts **30a–c** under the mentioned conditions, we isolated the products of the recyclization of salts **31a, b, c** such as 1,3-dihydro-4-diethyl (**32a**), 1,3-dihydro-4-dipropyl (**32b**), 1,3-dihydro-4-tetramethylenaminomethylphenanthreno[1,2-*c*]-furan (**32c**) with the yield of 45, 15 and 13 %, respectively. At the present moment it is difficult to vindicate the high yield (45 %) of the recyclization amine **32a**. Alongside with amines **32a–c** there were isolated such cyclization products as 2,2-diethyl- (**31a**) and 2,2-tetramethylene-4-hydroxymethylnaphtho[*f*]isoindolinium chlorides (**31c**) with the yield of 20 and 40 %, respectively. Owing to a good solubility of the cyclic salt **31b** the isolation thereof from the reaction mixture was impossible. By means of the conventional treatment of the mother liquor there can be cyclic salts **30a–c** isolated remaining in the solution, whose total yield values amount to 32, 65, and 67 %, respectively. All the attempts to obtain salt **31b** in the crystalline form were unsuccessful. In the case of direct performing the cyclization and recyclization of the salts **30a–c** with no isolation of cyclic products **31a–c** *via* stepwise adding 1.5 M KOH solution per 1 mol of the starting salt in water with heating the mixture at 78–80 °C for 1–1.5 h and the further extraction with ether, there were recyclization amines **32a–c** isolated from the reaction mixture with the total yield of 70–75 %. With no isolation of the cyclic products **31d, e** and **34a, b**, obtained by the cyclization of salts **30d, e** and **33a, b** under the conditions of base catalysis, the recyclization thereof was performed. As the result, there were recyclization amines **32d**, **32e**, **35a** and **35b** obtained with the total yield of 70–73 %.

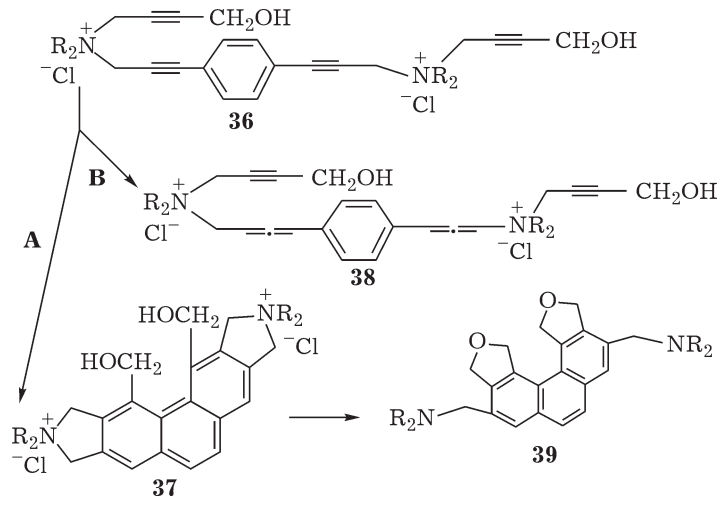
It is known that the recyclization of 2,2-dialkyl-4-hydroxymethylbenzo[*f*]isoindolinium chloride and 2,2-dialkyl-4-hydroxymethyl-6-chlorobenzo[*f*]isoindolinium chloride proceeds in the presence of double molar KOH amount per 1 mol of the starting salt *via* heating the mixture at 90–92 °C for 1.5–3 h [20, 25]. Comparing the recyclization conditions of the mentioned salts with the conditions of recyclization inherent in 2.2-dialkyl-4-hydroxymethylnaphtho[*f*]-isoindolinium analogues one could draw the following conclusion. Readiness for the recyclization of salts **31a–e** is caused by a higher electron-donor ability of the naphthalene ring as to compare with the benzene ring, which causes the electron density in the salt molecule to increase, thereby facilitating the attack of alkoxy anion onto a partially positively charged carbon atom of the isoindolinium cycle. As the result, there occurs breaking the N–C bond with the formation of C–O–C bond. In turn, the ease of recyclization the salts **34a,b** is, to all appearance determined by the presence of bulky substituents at the nitrogen atom, which makes the system unstable [28].

DOUBLE INTRAMOLECULAR CYCLIZATION OF AMMONIUM SALTS CONTAINING *p*-BIS(PROPYN-2-YL)BENZENE GROUP ALONGSIDE WITH 4-HYDROXYBUTYN-2-YL GROUP

It was established that salts **36** unlike 2-propinyl analogues [14, 32] under the conditions of base catalysis (salt/alkali = 2.5 : 1) exhibit transforming in two directions **A** and **B** [17, 30, 31] (Scheme 9).

In the case of direction **A** the salts **36** undergo double cyclization to form benzo[5,6:5′,6′-*a*,*c*]] [2,2-dialkyl-4-hydroxymethylisoindolinium] dichlorides **37** with the yield of 40–45 %.

The direction **B** corresponds to prototropic isomerization by 32–35 % and the formation of ammonium salts with allene group **38**, as indicated by the presence of absorption bands in the IR spectra within the range of 1930–1940 cm^{-1}. Separate experiments demonstrated that the salt **38** in the presence of aqueous alkali does not cyclise, whereas when heated in aqueous alkaline medium they exhibit polymerization. These data are consistent with the results of IR spectral studies [33–35] concerning



Scheme 9.

the cyclization mechanism, whereby enyne fragments are directly involved in intramolecular cyclization as π^4 fragment. Cyclic salts **37** can be isolated by means of filtration.

In a similar manner as the other salts [20, 23, 25, 28], the salt **37** under the conditions of base catalysis also exhibits recyclization to produce (6-dialkylaminomethyl-7,9,10,12-tetrahydro-8,11-dioxadicyclopenta[*c*,*g*]phenanthrene-1-yl-methyl) amines **39** with the yield of 7–9 %.

DOUBLE RECYCLIZATION OF BENZO[5,6:5′,6′-*a*,*c*][2,2-DIALKYL-4-HYDROXYMETHYLISOINDOLINIUM] DICHLORIDES

The authors of [25] and [28, 29] reported that the presence of chlorine atom in the aromatic ring, increasing the number of aromatic rings and of bulky substituents located at the nitrogen atom cause facilitating the recyclization. In order to establish the general nature of the phenomenon observed, we studied the ability of recyclization inherent in dichlorides 37 under the conditions of aqueous alkaline cleavage. It was established that salts 37 can be extremely readily subjected to double recyclization to form potentially bioactive dialkyl(6-dialkylaminomethyl-7,9,10,12-tetrahydro-8,11-dioxadicyclopenta[*c*,*g*]phenanthrene-1-yl-methyl)amine **39** with the yield of 70–72 % [31].

Upon the intermolecular recyclization of carbocyclic and especially heterocyclic compounds the ring opening of the parent molecule and the subsequent closure thereof can be realized under the action of various nucleophilic, electrophilic or dipolar reagents [36, 37]. The process is often accompanied by the expansion or contraction of the cycle, the introduction of heteroatom into the cycle or by replacing thereof with another heteroatom.

Unlike the intermolecular recyclization reactions, in the course of intramolecular recyclization revealed by E. O. Chukhajyan, A. R. Gevorkyan *et al.* [20], the disclosure of the parent molecule cycle occurs under the influence of intramolecular nucleophilic attacking by alkoxy anion formed in alkaline medium. The recyclization is not accompanied by neither extension nor contraction of the cycle, and instead of the five-membered ring there is isoindolinium pharmacophore dihydrofuran cycle formed. From the preparative point of view, the entire complex of transformations represents a one-stage reaction that makes it easy to synthesize various amino derivatives of dihydrofuran, *i. e.*, the compounds, whose synthesis *via* other chemical methods is difficult to perform. In order to confirm the importance of these amines from the standpoint of applications, it is enough to mention the fact that the hydrogenated phenanthrene cycle with the furan ring represents a part of the molecules of important naturally occurring alkaloids.

The structure of starting and cyclic salts, the recyclization amines was proved using IR spectral method, whereas the structure of cyclic salts and the recyclization amines was proved using also the methods of ^{1}H NMR and

^{13}C NMR. The assignment of signals in the ^{1}H NMR and ^{13}C NMR spectra was carried out basing on two-dimensional spectra such as COSY, NOESY, HMQC. The structure of 1,3-dihydro-4-diethylaminomethylnaphtho[1,2-*c*]furan bromomethylate [20], 2,2-dimethyl-4-α-naphthylbenzo[*f*]isoindolinium bromide [13] and *p*-phenylene-bis-4,4'(2,2-dimethylbenzo[*f*]-isoindolinium) dibromide [15] was also established by means of XRD structural analysis.

CONCLUSIONS

Basing on the studies performed in the field of base-catalyzed intramolecular cyclization it was demonstrated that quaternary ammonium salts containing two 3-phenylpropyn-2-yl groups, contrary to the literature, exhibit cyclization even in the absence of a base.

It was revealed that in the simultaneous presence of the ammonium salt of two different potentially diene groups in the molecule; the cyclization reaction is entered by 3-phenylpropyn-2-yl group as a diene component.

A sequence was revealed for the cyclization and dehydrochlorination reactions of ammonium salts containing chlorine atoms in the dienophile fragment. Bis-ammonium salts with *p*-bis(propyn-2-yl)benzene fragment under the conditions of base catalysis are subjected to double cyclization.

The cyclization of ammonium salts containing 4-hydroxy-butyn-2-yl group alongside with various enyne fragments occurs under much more severe conditions as to compare with propargyl analogues. It was revealed that the base-catalyzed intramolecular cyclization of ammonium salts containing various dienophile and potential diene fragments is of a general nature being a new field in the organic and fine organic chemistry, including huge synthetic potential for the formation of di-, tri- and polycyclic isoindolinium and dihydroisoindolinium salts containing different substituents either at the nitrogen atom and in the aromatic ring, as well as of important linearly annelated condensed nitrogen heterocycles.

It has been demonstrated that the substituents located at the nitrogen atom (methyl, ethyl tetramethylene, pentamethylene and bulky substituents) with no changing the direction of the reaction, which indicates the general character of the cyclization of salts containing β,γ-unsaturated groups alongside with the enyne fragments of various types, as well as the recyclization of 2,2-dialkyl-4-hydroxymethylisoindolinium salts and condensed analogues thereof.

Basing on the pharmacological studies, there were revealed the practical aspects of using the isoindolinium salts obtained those exhibit hypotensive, hypertensive, anticoagulant activity, as well as non-narcotic analgesic effects. There are also representatives with the complex of important pharmacological properties. The activity is protected by numerous author's certificates and patents of the USSR and Republic of Armenia.

It is demonstrated that the intramolecular recyclization of 4-hydroxymethylisoindolinium salts exerted by a beneficial effect of substituents in the aromatic ring, of increasing the number of aromatic rings, and of the presence of bulky substituents at the nitrogen atom. The intramolecular recyclization, in addition to the fundamental importance, leads to realizing wide opportunities for the synthesis of different dihydrofuran amino derivatives. It is known that the furan ring represents a piece of important naturally occurring alkaloid molecules. The structure of all the compounds obtained was established with the use of IR spectroscopy, ^{1}H and ^{13}C NMR spectrometry and XRD structural analysis in some cases.

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