NEW METHOD FOR THE SYNTHESIS OF POTENTIALLY BIOLOGICALLY ACTIVE ISOINDOLINIUM AND DIHYDROISOINDOLINIUM SALTS AND THEIR CONDENSED ANALOGS (REVIEW)

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The base-catalyzed intramolecular cyclization of the diene-synthesis type of quaternary ammonium salts, which leads to potentially biologically active isoindolinium and dihydroisoindolinium salts and their condensed analogs, is examined. The alkaline cleavage of the products, a possible reaction mechanism, and the results of biological tests are discussed.

Extensive research on the thermal intramolecular cyclization of systems that include 1,3-diene fragments has been carried out in recent years, since it is becoming evident that this reaction can be successfully used for the synthesis of numerous interesting bridged compounds, including many natural substances [1, 2]. The literature contains only a few reports of the base-catalyzed intramolecular cyclization of systems that contain enyne fragments as potentially diene fragments [3-7].

The present review paper is the first in which research on the base-catalyzed intramolecular cyclization of ammonium salts that contain β,γ-unsaturated groups in addition to enyne fragments [3-alkenyl(or aryl)propargyl groups] and the aspects of obtaining potentially biologically active isoindolinium and dihydroisoindolinium salts and their condensed analogs on the basis of this reaction are discussed. The cyclization–dehydrochlorination of ammonium salts with a 2,3-dichloro-2,4-pentadienyl or 3-aryl-2,3-dichloroallyl group, which leads to chlorine-containing isoindolinium salts, is also examined. The alkaline cleavage of the cyclic salts obtained, which leads to aliphatic, aromatic, and heterocyclic amines, a possible mechanism of the cyclization, and the results of biological tests are discussed.

I. CYCLIZATION OF AMMONIUM SALTS CONTAINING 3-ALKENYL(ARYL)PROPARGYL GROUPS AS POTENTIALLY DIENE FRAGMENTS LEADING TO DIHYDROISOINDOLINIUM AND ISOINDOLINIUM SALTS AND THEIR CONDENSED ANALOGS

I.1. Cyclization—Cleavage of Allyl(or propargyl)dialkyl (3-alkenylpropargyl)ammonium Salts

The intramolecular cyclization—cleavage of ammonium salts to give dialkylaminomethyl derivatives of aromatic compounds was discovered by Babayan and Tagmazyan [8-10]. In 1964 Babayan and coworkers demonstrated that ammonium salts I, which, in addition to a grouping of the allyl type, contain a 3-alkenylpropargyl grouping, on reaction with aqueous alkali undergo intramolecular cyclization—cleavage to give N,N-dialkylbenzylamines with substituents in the ring [11, 12]. They assumed that cleavage of ammonium salts I is preceded by intramolecular cyclization of the diene-synthesis type, leading to 2,2-dialkyldihydroisoindolinium complexes Ia, the cleavage of which leads to N,N-dialkylbenzylamines.

It was established that the alkaline cleavage of salts Ia proceeds basically via the 1,2 pathway. To distinguish this reaction from ordinary aqueous-alkaline cleavage of ammonium salts it was called cyclization—cleavage, since cleavage is

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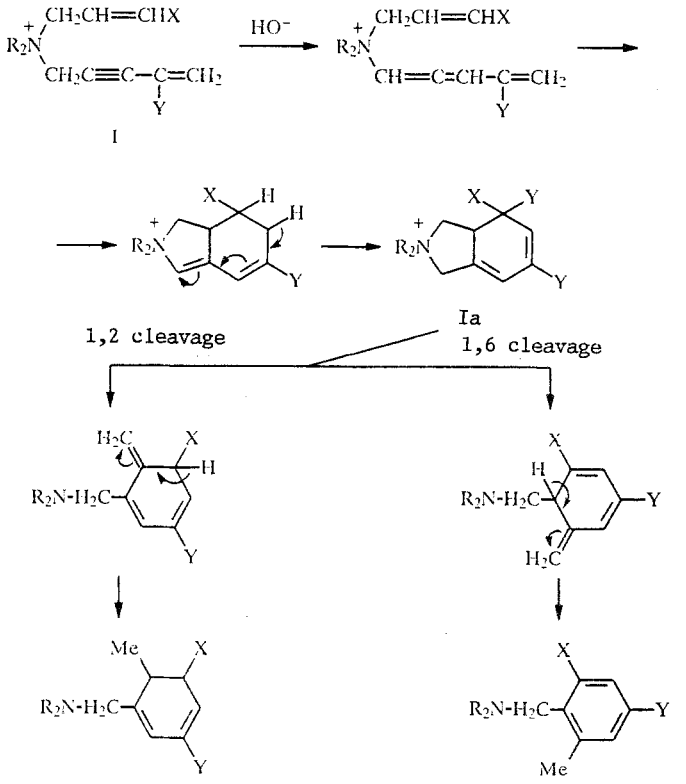
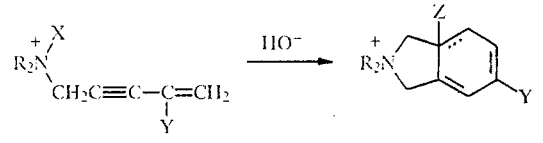


preceded by cyclization. When β position of the allyl group of starting salt I contains a methyl substituent, which excludes the possibility of 1,2 cleavage, aromatization of the cyclohexadiene ring is realized by direct cleavage of the C–C bond [13-15].

Salts that contain a 3-Δ'-cyclohexenylpropargyl group in addition to a group of the allyl type undergo cyclization—cleavage reactions [12].

Proceeding from the fact that alkali is not consumed in the cyclization process, it was established that the cyclization of salts I and II, which contain groups of the allyl or propargyl type in addition to a 3-alkenylpropargyl group, is realized with heat evolution in the presence of catalytic amounts of aqueous alkali [16-18].



I, II I, IIa

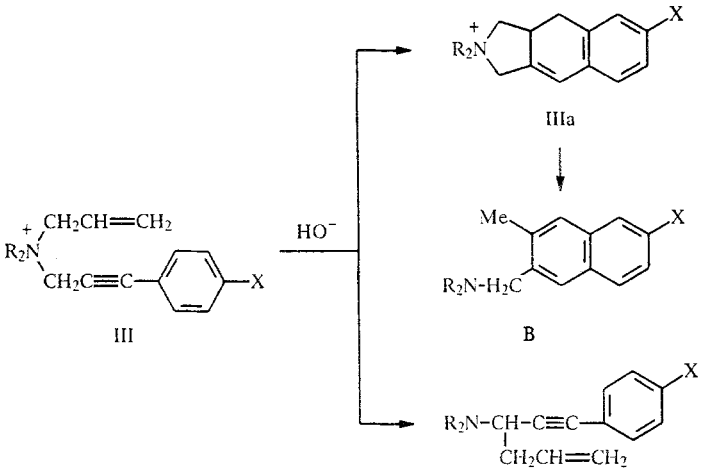
I X = —CH_2—CZ=CH_2, Y = Z = H, Me; II X = —$CH_2C\equiv CH$, Y = H, Me, R^2 = Me_2, Et_2, $(CH_2)_5$, $(CH_2)_2O(CH_2)_2$

As a result, dihydroisoindolinium (Ia) and isoindolinium (IIa) salts, the synthesis of which is difficult to accomplish by other methods, are formed in almost quantitative yields.

I.2. Cyclization of Ammonium Salts with a 3-Arylpropargyl Group to Give Dialkyldihydrobenzisoindolinium Salts

In 1963 Iwai and Hiraoka studied the reaction of allyl(dimethyl)(3-phenylpropargyl)ammonium bromide with dilute aqueous sodium hydroxide in order to obtain a product of the Stevens rearrangement [19]. They isolated only a product of the Stevens rearrangement in 22% yield. On the basis of research on the base-catalyzed intramolecular cyclization of ammonium salts one might have expected the formation of a cyclization product [16-18]. However, the cyclization product escaped the attention of the researchers, since, under the conditions of their experiment, it does not undergo subsequent cleavage and remains in aqueous solution. It was established that intramolecular cyclization (12%) and rearrangement—cleavage (8%) take place along with the Stevens rearrangement (40%) under similar conditions [20].

In contrast to the 3-alkenylpropargyl analogs, cyclization—cleavage products (B) are obtained in low yields in the direct aqueous-alkaline cleavage of ammonium salts that contain a 3-arylpropargyl group in addition to a group of the allyl type; the principal pathway is the Stevens rearrangement [20].

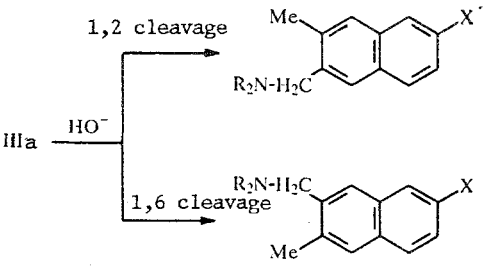


X = H, Me, Cl, R = Me, R = Et, R = $(CH_2)_3$, R = $(CH_2)_2O$

Cyclization—cleavage products B are obtained in high yields by heating aqueous solutions of the salts in the presence of traces of aqueous alkali with subsequent cleavage of the cyclization products [20]. A handy method for obtaining dihydrobenzisoindolinium salts IIIa was developed under the conditions of basic catalysis of the cyclization of salts III that contain an allyl group in addition to a 3-arylpropargyl group [20-22].

The course of the reaction changes markedly when there is a methyl substituent in the β position of the allyl link. Thus salts that contain a methallyl group in addition to a 3-phenylpropargyl group do not undergo cyclization under base-catalysis conditions but primarily undergo rearrangement—cleavage (60-65%) and the Stevens rearrangement (5-8%) [23]. The rearrangement—cleavage of the above-indicated salts is catalyzed by the action of the secondary amines formed as a result of the reaction. Rearrangement—cleavage reactions (40-50%) and the Stevens rearrangement (16-20%) take place in the reaction (with heating) of these salts with a twofold molar amount of potassium hydroxide in aqueous solution; a cyclic compound was not obtained. The transformations of an allyl(dimethyl)(3-phenylpropargyl)ammonium salt were studied by Laird and Ollis at a considerably later date, and the results were similar [24, 25].

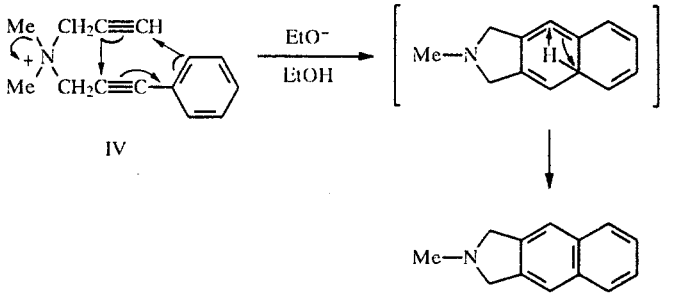
The alkaline cleavage of dialkyldihydrobenz[f]isoindolinium salts IIIa may proceed via a 1,2 or a 1,6 pathway. One cannot exclude the possibility that the process takes place via both pathways simultaneously.



A handy method for obtaining chromatographically pure dialkylaminomethylnaphthalenes in 60-73% yields was developed on the basis of the aqueous-alkaline cleavage [20-22].

I.3. Cyclization of Dialkyl(propargyl)(3-arylpropargyl)ammonium Salts

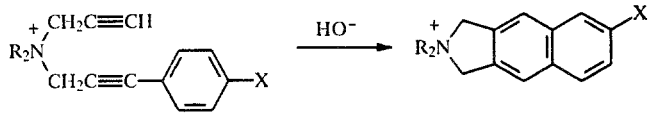
An interesting intramolecular cyclization—cleavage reaction was observed by Iwai and Hiraoka in a study of the reaction (with heating) of dimethyl(propargyl)(3-phenylpropargyl)ammonium ion IV with sodium ethoxide in ethanol [26]. In the reaction products they detected 2-methylbenz[f]isoindoline (C) (in ≈20% yield), the formation of which they represented by a scheme that includes cyclization with synchronous splitting out of a methyl group and subsequent aromatization of the 1,2,4-cyclohexatriene ring as a result of isomerization.



IV

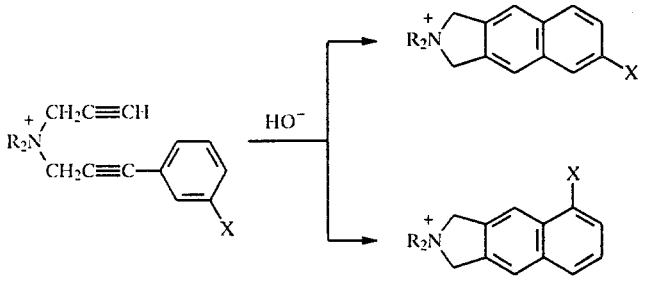
In the proposed scheme, the step involving direct intramolecular cycloaddition with the participation of the propargyl and 3-phenylpropargyl groups with the intermediate formation of a cyclohexatriene ring with an allene system of bonds is unlikely. On the basis of the results obtained for the intramolecular cyclization of ammonium salts [16, 17, 20], one might have assumed that the primary reaction product is dimethylbenz[f]isoindolinium bromide (IVa), cleavage of which leads to the amine. Repetition of the experiment with changes only in the extraction of the reaction products showed that the principal product is actually 2,2-dimethylbenz[f]isoindolinium bromide (50%), cleavage of which gave methylbenz[f]isoindoline [18, 27].

As one should have expected, benzisoindolinium salts are formed in almost quantitative yields in the case of salts that contain a propargyl group in addition to a 3-arylpropargyl group under the conditions of basic catalysis, which excludes the possibility of nucleophilic substitution [16-18, 21, 22, 28].



R = Me, R = Et, R = $(CH_2)_2$, R = $(CH_2)_3$, R = $(CH_2)_2O$, X = H, X = Me, X = Cl

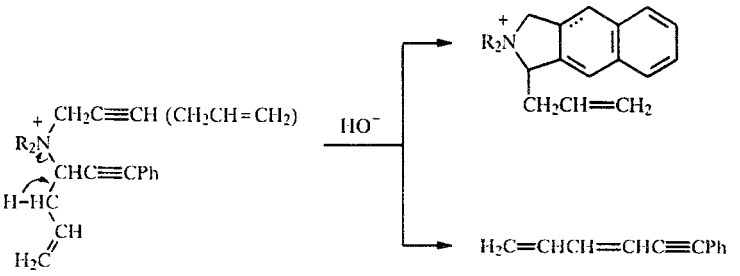
When substituents are present in the meta position of the aromatic ring, cyclization is realized both in the ortho and para positions of the aromatic ring with respect to the substituent [29].



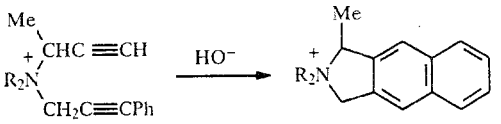
X = Me, Cl

Cyclization of salts of the IV type is also realized in the presence of amines (diethylamine and triethylamine) but with heating.

When there is an allyl substituent in the 1 position of the 3-phenylpropargyl group, β cleavage (10-15%) occurs along with cyclization (56-63%) [30].



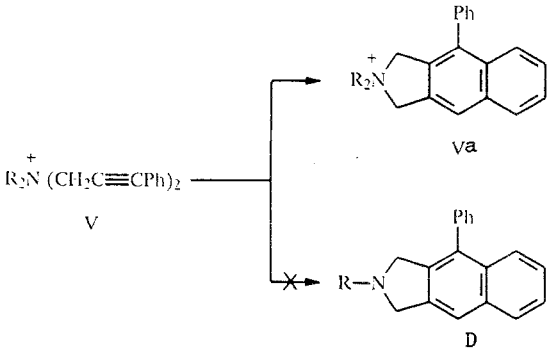
An α-methylpropargyl group was also involved as a β,γ-unsaturated group in the cyclization [29].



The same compounds as those obtained in the case of the 2-butyl group are obtained in the case of participation of the 3-chloro-2-butenyl group in the cyclization [31-33]. Cleavage primarily takes place in the case of the dimethyl(3-chloro-5-methoxy-2-pentenyl)(3-phenylpropargyl)ammonium ion as a consequence of the ease of splitting out of the 3-chloro-5-methoxy-2-pentenyl group. A cyclic compound is obtained in 20% yield [33]. Cyclization is the predominant pathway for dimethyl(3-chloro-5,5-dimethyl-2-hexenyl)(3-phenylpropargyl)ammonium chloride, since the tertiary butyl radical decreases the lability of the hydrogen atom in the δ position of the 3-chloro-2-butenyl group, as a consequence of which cleavage is hindered [33].

I.4. Cyclization of Salts with Bis(3-Enyne) Groups

In a study of the reaction of dimethylbis(3-phenylpropargyl)ammonium bromide (V) with sodium ethoxide in ethanol Iwai and Hiraoka expected the formation of 2-methyl-4-phenylbenz[f]isoindoline (D). Despite their expectations, an amino compound was not formed. Proceeding from this, it was concluded that the salt tested, because of unfavorable steric factors, does not undergo cyclization—cleavage [19, 26]. However, on the basis of other research [16-18, 20] one might have expected the formation of a cyclization product — 2,2-dimethyl-4-phenylbenz[f]isoindolinium bromide (Va) rather than free amine D.



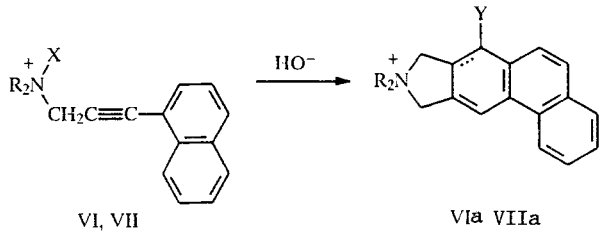
It was established that both the dimethylammonium salt and salts with other alkyl groups attached to the nitrogen atom undergo quantitative cyclization with heat evolution even in the presence of traces of aqueous alkali [34-37] to give condensed isoindolinium analogs. Salts with bis(3-alkenylpropargyl) groups also undergo smooth cyclization under base-catalysis

conditions. A report regarding the possibility of cyclization of salt V was published later [24]. The above-indicated salts also undergo cyclization in the absence of a base when aqueous solutions of them are heated.

A handy method for obtaining isoindolines and benzisoindolines in high yields was developed by aqueous-alkaline cleavage of isoindolinium and benzisoindolinium salts that contain a group that is easily eliminated attached to the nitrogen atom [18, 21, 28, 36, 37].

I.5. Cyclization of Ammonium Salts with a 3-α-Naphthylpropargyl Group

Salts VI and VII, which contain groups of the propargyl or allyl type in addition to a 3-α-naphthylpropargyl group, undergo cyclization under base-catalysis conditions [38-41].

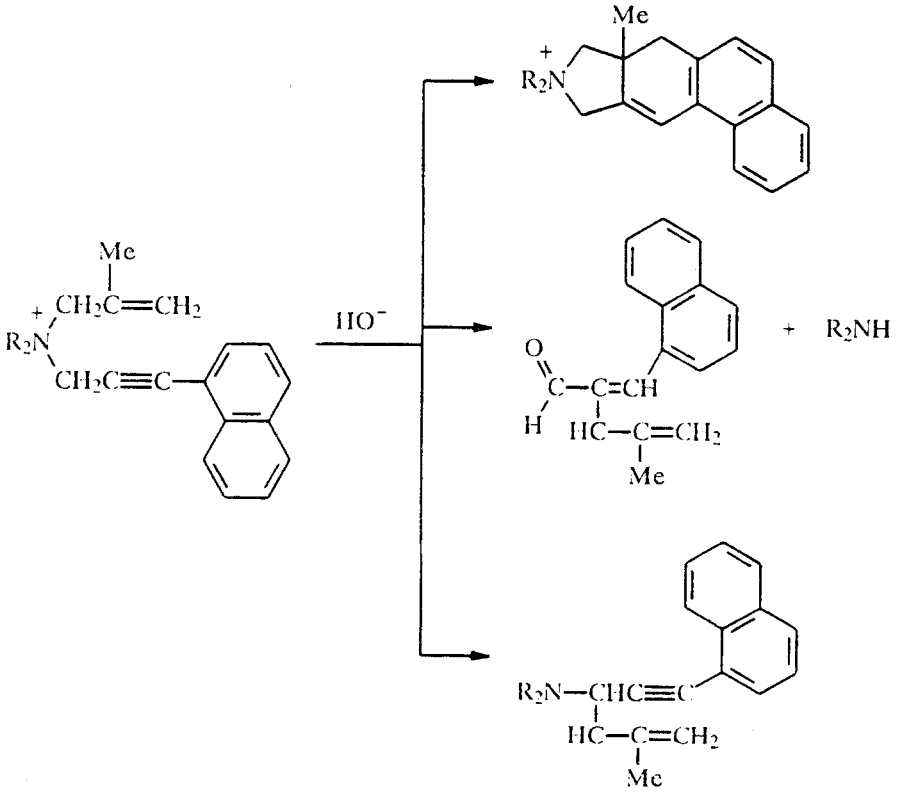


VI, VII VIa VIIa

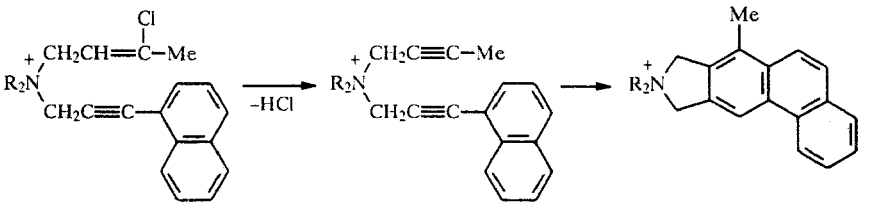
VI X = —CH_2—C≡C—Y; VII X = —CH_2=C=CH_2; Y = H, α-naphthyl

The cyclization of propargyl analogs proceeds with heat evolution. The yields of dialkylnaphth[f]isoindolinium (VIa) and -dihydronaphth[f]isoindolinium (VIIa) salts are quantitative. Heating at 90°C for 2 h is required for allyl analogs. The cyclization of bis(3-α-naphthylpropargyl) salts also proceeds in the absence of a base by heating aqueous solutions of them [41].

In contrast to dialkyl(methallyl)(3-phenylpropargyl)ammonium salts [23], the methallyl analogs of the above-indicated salts primarily undergo cyclization (54-60%). Rearrangement—cleavage (8-10%) and the Stevens rearrangement (5-8%) also occur along with cyclization [42].

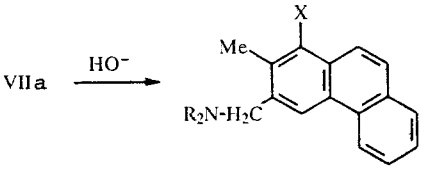


Salts VIII with a 3-chloro-2-butenyl group undergo dehydrochlorination—cyclization in an aqueous-alkaline medium at room temperature to give dialkyl-4-methylnaphth[f]isoindolinium salts VIIIa [43, 44].



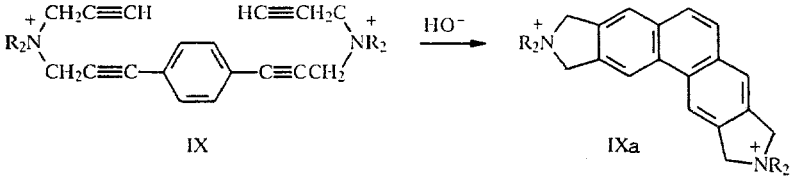
VIII VIIIa

The aqueous-alkaline cleavage of dihydronaphth[f]isoindolinium salts leads to dialkylaminomethylphenanthrenes [38].



I.6. Cyclization of p-Bis[3-(dialkyl-2-propynyl-ammonio)-1-propynyl]benzene Dibromide

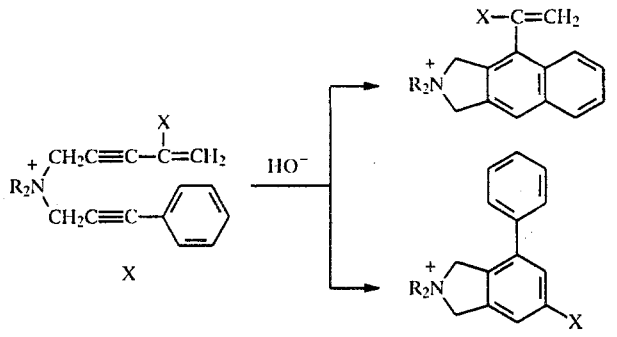
In the case of the presence of two reaction centers in quaternary ammonium salt IX, which contains a p-(bispropargyl)benzene fragment, the phenomenon of double cyclization, which leads to bisisoindolinium salts IXa, was observed [45].



IX IXa

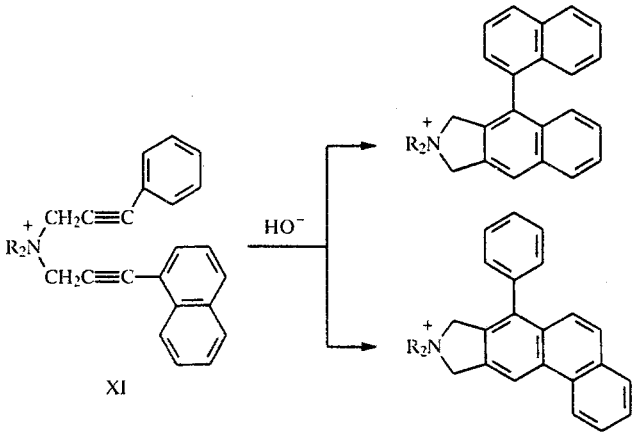
II. COMPETITIVE REACTIVITIES OF VARIOUS GROUPS

On the basis of the research one might conclude that the 3-alkenylpropargyl group, as one should have expected, with respect to its reactivity as a diene surpasses the 3-phenylpropargyl group [20, 23], while the 3-α-naphthylpropargyl group occupies an intermediate position [42]. In a comparison of the dienophilic capacities of the allyl and propargyl groups the activity of the latter was revealed. The fact that the propargyl group acts as a dienophile when allyl and propargyl groups are simultaneously present in the molecule along with a 3-phenylpropargyl group serves to confirm this [28]. Similar results were obtained in [46, 47]. However, in the case of the simultaneous presence of 3-phenylpropargyl and 3-alkenylpropargyl groups in ammonium salt X or of 3-phenylpropargyl and 3-α-naphthylpropargyl groups (in salt XI) the reaction proceeds with the primary participation of the 3-phenylpropargyl group as the potential diene [37, 48]. Similar results were obtained by Laird and Ollis in the cyclization of 3-isopropenylpropargyl 3-phenylpropargyl ether [4].(See top of next page.)



X

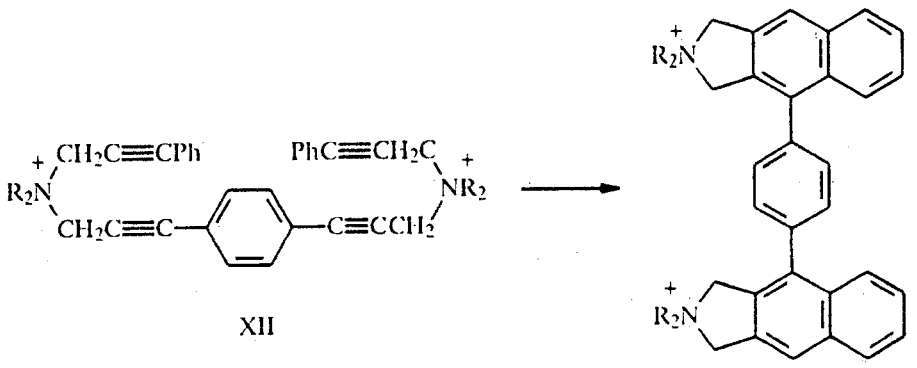
X = H, Me



XI

R^2 = Me_2, Et_2, $(CH_2)_5$

In the case of the presence of 3-phenylpropargyl and p-(bispropargyl)benzene groups in ammonium salt XII the 3-phenylpropargyl group also acts as a diene in the cyclization [49].



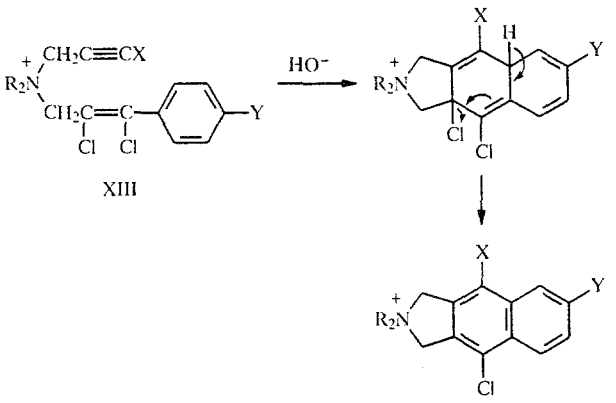
XII

XIIa

III. SYNTHESIS OF CHLORINE-CONTAINING ISOINDOLINIUM AND BENZISOINDOLINIUM SALTS BY CYCLIZATION—DEHYDROCHLORINATION OF AMMONIUM SALTS

III.1. Cyclization—Dehydrochlorination of Dialkyl(propargyl) (3-aryl-2,3-dichloroallyl)ammonium Salts

Salts XIII, which contain a group of the propargyl type in addition to a 3-aryl-2,3-dichloroallyl group, undergo cyclization—dehydrochlorination in the presence of 1.2 moles of aqueous alkali at room temperature. As a result, chlorine-containing benzisoindolinium salts XIIIa are formed [50-53].



XIII

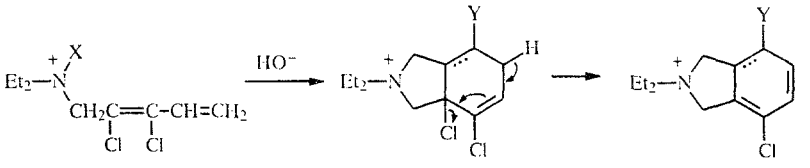
XIIIa

R^2 = Me_2, Et_2; X = H, $-CH=CH_2$, Ph; Y = H, Cl

III.2. Cyclization of Ammonium Salts with a 2,3-Dichloro (or 3,4-Dichloro)-2,4-pentadienyl Group

Salts XIV and XV, which contain a propargyl group or a group of the allyl type in addition to a 2,3-dichloro-2,4-pentadienyl group, undergo cyclization—dehydrochlorination in the presence of 1.2 moles of aqueous alkali with heat evolution to give chlorine-containing isoindolinium (XIVa) and dihydroisoindolinium (XVa) salts [51, 54].

The above-indicated salts also undergo cyclization in the absence of a base.

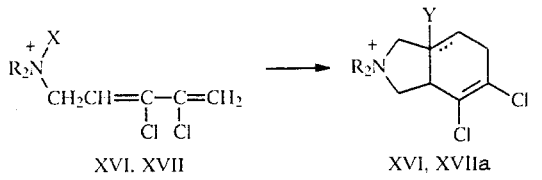


XIV, XV

XIV, XVa

XIV X = $-CH_2C\equiv CH$; XV X = $-CH_2-CH=CH-Y$, Y = H, Me

Salts XVI and XVII with a 3,4-dichloro-2,4-pentadienyl group undergo cyclization only in the absence of a base by heating solutions of them in water or dimethylformamide to give dialkyldihydro- (XVIa) and -tetrahydroisoindolinium (XVIIa) salts containing two chlorine atoms in the ring [55].

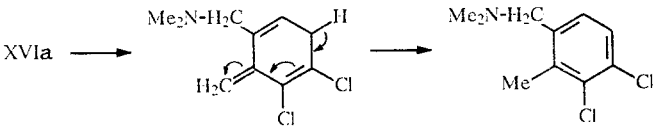


XVI, XVII XVI, XVIIa

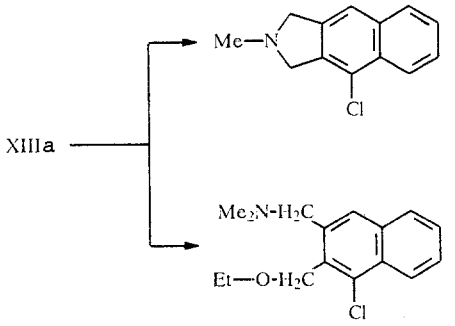
XVI X = $-CH_2-C\equiv CH$; XVII X = $-CH_2-CY=CH_2$; Y = H, Me; R = Me, Et

The aqueous-alkaline cleavage of 4-chloro-2,2-diethylisoindolinium salt XIVa leads to a chlorine-containing isoindoline [54]. The cleavage of dihydroisoindolinium analog XVa of the above-indicated salt proceeds smoothly under the influence of sodium ethoxide [54].

The aqueous-alkaline cleavage of 4,5-dichloro-2,2-dimethyl-3*a*,6-dihydroisoindolinium bromide (XVIa) proceeds very smoothly and leads to the chromatographically pure amine in 82% yield [55].



Only nucleophilic splitting out of the N-methyl group occurs when there is a substituent in 4-chlorobenzisoindolinium complex XIIIa. Both nucleophilic splitting out of the N–C bond of the isoindolinium ring occur in the absence of a substituent [50, 51].

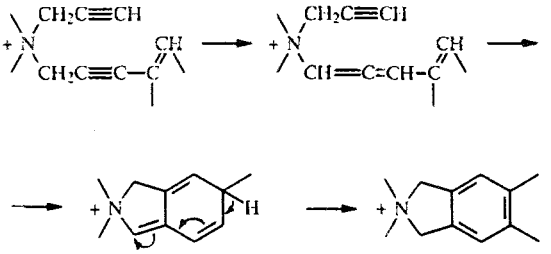


On the basis of the research carried out it was established that the base-catalyzed intramolecular cyclization of ammonium salts that contain various potentially diene and dienophile fragments is general in character and that this new pathway opens up tremendous synthetic possibilities for obtaining potentially biologically active isoindolinium and dihydroisoindolinium salts and their condensed analogs containing various substituents attached to both the nitrogen atom and the aromatic ring.

IV. POSSIBLE MECHANISM OF THE CYCLIZATION OF DIALKYL(PROPARGYL)[3-ALKENYL(OR ARYL)PROPARGYL]AMMONIUM SALTS

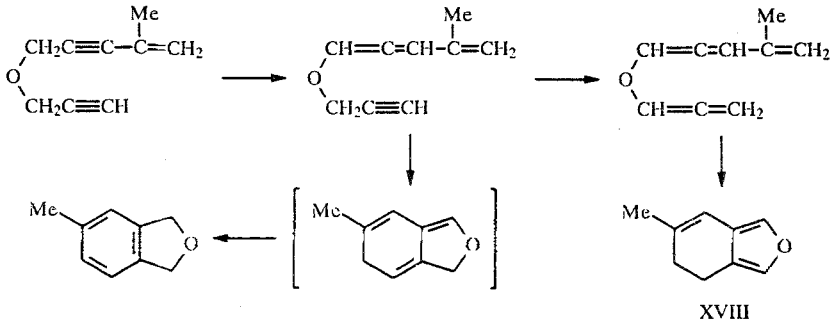
Kinetic investigations devoted to the study of the effect of structural and external factors on the cyclization of salts haveshown that a mechanism that includes steps involving isomerization and cyclization of the isomerized salt and aromatization of the cyclization product is most probable [56-63].

Scheme 1



This is in agreement with the literature data on the cyclization of acetylenic compounds [3-7]. In the opinion of the researchers [3-5], the base-catalyzed cyclization of compounds with the general formula $X(CH_2C{=}CC_6H_5)_2$, as well as allyl ethers of isopropenylpropargyl and phenylpropargyl alcohols, proceeds through α-allene isomerization with subsequent cyclization. The formation of isobenzofuran XVIII serves as evidence that allene formation precedes cyclization in these reactions [5].

Scheme 2



XVIII

The assumption that allene derivatives may be intermediates in various reactions is in agreement with observations relative to the ease of isomerization of acetylene derivatives to allene derivatives. The isomerization of acetylenic compounds proceeds particularly readily in cases in which the propargyl methylene group is connected to electron-acceptor groups [64-71].

All of these data constitute evidence in favor of Scheme 1, which includes isomerization of the 3-aryl- or 3-alkenylpropargyl group to a 3-aryl- or 3-alkenylallenyl group, since favorable conditions for isomerization exist in the salts tested: the electronegative inductive effect of the ammonium ion and the presence of an alkenyl or aryl group in the 3 position of the propargyl group. The fact that the cyclization of salts that contain already existing 1,3-conjugated systems in addition to groups of the allyl or propargyl type is realized in the absence of basic agents by heating solutions of them [72-74] constitutes evidence that the catalytic action of alkali in 3-aryl- or 3-alkenylpropargyl systems consists primarily precisely in the isomerization process.

V. RESULTS OF BIOLOGICAL STUDIES

To ascertain the practical aspects of the use of isoindolinium and dihydroisoindolinium salts, as well as their condensed analogs, in medical practice biological testing of them has been carried out in many science centers. It was found that isoindolinium and dihydroisoindolinium salts have hypertensive activity, stimulate respiration over a long period of time, and may have great promise under clinical conditions, in which a decrease in the arterial pressure in various infections,

intoxications, and collaptoidal states has been noted [75-77]. Condensed analogs of these salts have pronounced hypotensive activity and may find application in hypertension with disruption of the nourishment of individual circulatory zones, particularly the brain, since they are effective with respect to brain vessels.

Among the compounds obtained there are representatives with analgesic activity that is non-narcotic in character; this is especially important, since the problem of the search for effective analgesics in medicine remains acute and requires further purposeful research. A number of the compounds obtained have a set of important properties: they have a significant anti-aggregation effect on human blood and have analgesic, choline-sensitizing, cardiotonic, and hypotensive activity. With the respect to their strength and the duration of their activity these compounds surpass lobeline, papaverine, Dibasole, amidopyrine, K-strophanthin, and aspirin.

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