UTILIZATION OF AMINOMERCURATION

AND HYDROXYMERCURATION REACTIONS

IN THE SYNTHESIS OF HETEROCYCLES (REVIEW)*

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The cyclization of ethyleneamines by the action of mercury salts to give five- and six-membered nitrogen heterocycles is examined. The mechanism and stereochemistry of this reaction and the chemical and three-dimensional structures of the intermediate organomercury compounds and some chemical properties of the latter are discussed.

Beginning in 1966, we developed a new method for the alkylation of amines by olefins by means of mercury salts; this method has also found application in the synthesis of nitrogen heterocycles [1].

In the present communication some general problems of reactions proceeding with intramolecular cyclization (see the review in [2]) will be examined briefly. Special attention will be directed to the peculiarities of mercury-containing electrophilic reagents and to the properties (in particular, the stereochemical properties) of the intermediate organomercury compounds. The principal portion of this review is devoted to heterocyclization by means of aminomercuration. Hydroxymercuration and aminomercuration reactions will be compared at the end of this review.

Cyclization in two possible directions can occur simultaneously when electrophilic reagent XZ is added to an unsaturated molecule having an electron-donor grouping:
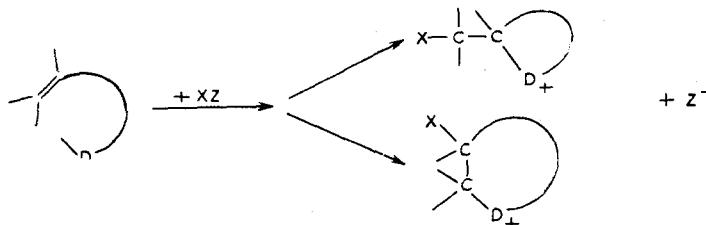
This sort of cyclization is a special case of reactions involving the participation of adjacent groups, which, in conformity with certain stereochemical peculiarities, lead to rings of definite structure. With a few exceptions, rings of this sort usually have five to six links. The predominant orientation corresponds to the classical principles of electrophilic addition (for example, to the Markownikoff rule).

The structure of the cyclization product depends on the character of the substituents attached to the double bond, on steric effects, which influence the stabilization of the cyclic transition state, and on the nucleophilic properties of the electron-donor portion of the unsaturated molecule. The nature of the electrophile and the solvent used also may have a definite effect.

When two substituents are attached to the terminal carbon atom of the double bond, a six-membered ring is formed, whereas when another carbon atom is substituted a five-membered ring is obtained.

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An additional factor is the configuration of the molecule: It is known that the orientation of cyclization in a number of cinnamic acids changes as the geometry of the double bond is altered.

If there is yet another heteroatom in the chain of the unsaturated molecule ($CH_2 = CH - CH_2 - Z - CH_2CH_2 - D$, $Z = O, S, NH$), the degree of cyclization decreases. Moreoever, the reaction is inhibited and is sometimes replaced by an addition or substitution reaction. This effect is particularly noticeable when oxygen is the second heteroatom.

Iodine, Br_2, Cl_2, Hg^+, peracids, etc., are used as the electrophilic reagents. In order to avoid competition with normal addition reactions, it is expedient to use weak electrophiles (I_2, $HgCl_2$), particularly in nonaqueous solutions. It has been shown (Berti) that, for example, trans-2-carboxy-stilbene is cyclized completely when it is treated with chlorine in all nonaqueous solvents, whereas bromine brought about cyclization in $CHCl_3$ but added to the substrate in CCl_4. When water is used as the solvent, the opposite pattern is observed. Sometimes electrophilic reagents may participate in the cyclization reaction in different forms ($HgCl_2 \rightarrow HgCl_2$ and $HgCl^+$); $HgCl^+$ is 120,000 times more reactive than the neutral molecule.

Kinetic investigations indicate that (1) the rate of cyclization depends on the structure, configuration, and conformation of the unsaturated portion of the molecule and the ratio between the electrophilic properties of the reagent and the nucleophilic properties of the donor group; (2) alkyl substituents at the end of the chain accelerate the reaction; (3) aromatic substituents inhibit the reaction.

The mechanism of the reaction consists in the formation of onium structures with subsequent trans addition. It should be noted that reactions of this sort are much more sensitive to nucleophilic properties of the donor substituent than the usual addition reactions.

Mercury Salts as Electrophilic Reagents and Some Properties of Organomercury Compounds

The electrophilic properties of mercury salts change as a function of the nature of the anion; thus mercuric acetate is a stronger electrophile than mercuric chloride.

One of the isotopes of mercury (^{199}Hg, spin $1/2$, natural abundance 17%) has rather large spin−spin constants for coupling with vicinal and geminal protons, and this makes organomercury compounds convenient materials for NMR investigations.

Organomercury compounds are considerably less reactive than many other organometallic compounds. This is due to the small amount of ionic character of the metal−carbon bond (11%); this is explained by the fact that the electronegativity of mercury (1.95) is very close to the electronegativity of carbon.

The products of addition of mercury salts to π bonds are of particular interest. They have been known since 1892 [3, 4] and have been thoroughly investigated in connection with the fact that they are important intermediates in organic synthesis. The reaction of a mercury salt with a double bond usually gives either an addition product (path a) or an allyl substitution product (path b):
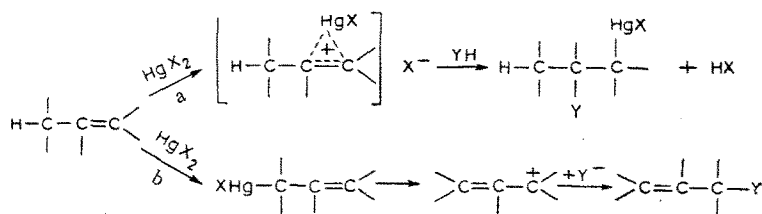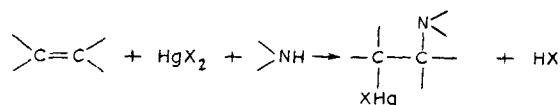

Addition has been accomplished primarily by means of hydroxyl-containing reagents — water, alcohols, acids, peracids, etc. — and has been called the hydroxymercuration reaction [5].

We extend the boundaries of applicability of these mercuration reactions by using primary and secondary amines as the nucleophiles and in this way realizing aminomercuration. Several studies that preceded our investigations in this area should be mentioned [6-8].

Aminomercuration − Intramolecular Heterocyclization of Ethyleneamines

Depending on the types of olefin and amine, this reaction may be either a method for alkylation of amines (after demercuration of the intermediate) or a method for amination of a double bond.

$$\text{>C=C<} + \text{HgX}_2 + \text{>NH} \longrightarrow \underset{\text{XHg}}{-\overset{|}{\text{C}}-}\overset{\overset{\text{N<}}{|}}{\underset{|}{\text{C}}}- + \text{HX}$$

The reaction has ionic character. A π complex or a mercurinium ion is formed in the first step, and a Markownikoff addition product is obtained when it reacts with an amine.

The reduction of the intermediate organomercury compound with complex hydrides proceeds via a radical or ionic mechanism. In the latter case, an aziridinium ion is formed as an intermediate structure, and this sometimes leads to the production of two isomeric amines.

The structure of the organomercury compound can be established by NMR spectroscopy from the $J_{\text{199Hg,H}}$ value.

If the double bond and the amino group are located in the same molecule and are separated by a sufficiently long carbon chain, aminomercuration proceeds intramolecularly via the same scheme to give a heterocycle containing one less carbon atom:
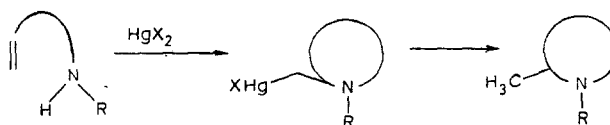

Reactions of this sort are known in the case of hydroxymercuration. Thus in 1923 Adams realized the cyclization of o-allylphenol with mercury salts to a mercurated dihydrobenzofuran [9]:
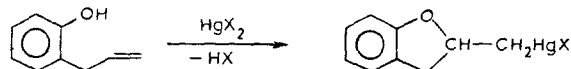
The kinetics of this reaction were investigated in [10], and later, with the use of other ethylene alcohols, it became a method for the synthesis of numerous furan and pyran derivatives [11]. The same type of cyclization was examined in [12].

The investigation of intramolecular aminomercuration has developed in several directions: the study of the effect of solvents, the effects of a change in the nucleophilicity of the nitrogen atom as the substituent attached to this atom is varied, and establishment of the effects of modification of the carbon skeleton (substitution in the chain or at the double bond, and change in the chain lengths).

The intramolecular cyclization of 1-propylamino-4-pentene (I) in an aprotic solvent [tetrahydrofuran (THF)] by means of mercuric chloride gave, after reduction of intermediate organomercury compound II, individual 1-propyl-2-methylpyrrolidine (III) in 80% yield.
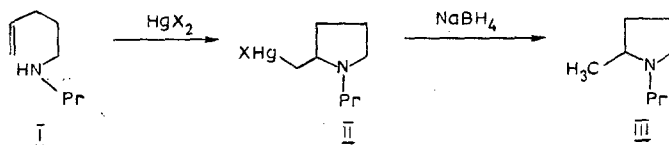
Although the organomercury compound was not isolated because of its instability, the formation of only pyrrolidine II as a result of reduction indicates that primary attack of the mercury cation proceeds at the terminal carbon atom.

In order to verify whether the stoichiometry of intermolecular aminomercuration (amine/ $\text{HgX}_2 = 2$) is retained in this case, the cyclization was investigated by means of NMR spectroscopy. It was found that when the amine-to-mercury salt ratio is unity, the signals of the ethylene protons vanish completely. The formation of an organomercury compound is confirmed also by the appearance of the signal of a proton attached to a tertiary carbon atom and by a characteristic shift of the other signals. Thus, the proton that is released as a result of cyclization remains fixed in the reaction product and does not add to the starting amine.

It was shown by a special experiment that in the alkaline medium in which the reduction with sodium borohydride is performed, the organomercury compound is stable, in contrast to the previously reported data [5].

TABLE 1. Yields of the Product of Cyclization of 1-Propylamino-4-pentene by Means of Mercuric Chloride

Solvent	THF	H_2O	THF/H_2O	MeOH	AcOH
Yield, %	75	80	85	85	10

TABLE 2. Yield of Cyclization Products of N-Substituted 1-Amino-4-pentenes (mercuric chloride in THF)

Amine	IV	V	I	VI	VII
R	H	Me	Pr	t-Bu	Ph
Yield, %	20*	50	75	60	0

* The yield was 70% when mercuric acetate was used.

Replacement of mercuric chloride by the acetate does not affect the direction of the cyclization of amine I, but this replacement is of significance for reactions with primary ethyleneamines.

Aprotic solvents, which make it possible to avoid competetive hydroxymercuration, were the most convenient solvents initially. Most of the cyclization reactions were therefore carried out in THF, in which mercuric chloride dissolves readily, whereas most of the resulting cyclic organomercury compounds are only slightly soluble in it, and this is of additional interest from a preparative point of view.

Although it was assumed that hydroxymercuration would proceed at a high rate in a protic medium, the reaction in water, methanol, or even in acetic acid gave exclusively an intramolecular aminomercuration product. The cyclization should therefore be considered to be mercuration of the double bond with participation of the adjacent nitrogen atom (anchimeric acceleration). This sort of participation is a maximum if a five-membered ring is formed, as has been found for the solvolysis of chlorohydrins [13].

In addition, it is known that this sort of participation shows up most distinctly if two groups are in an anti conformation [13]. The assumption of an anti orientation of the nitrogen and mercury atoms in the transition state of the cyclization follows from this.

From a preparative point of view, THF, methanol, or water are approximately identically suitable for the cyclization. On the other hand, in acetic acid the yield of cyclization product is low because of partial protonation of the nitrogen atom of the starting amine (Table 1).

The best results were obtained when the reaction was carried out in THF/H_2O; this was also noted in the case of hydroxymercuration [14].

Substituents attached to the nitrogen atom of the unsaturated amine may affect the course of intramolecular aminomercuration. This effect may be both a polar and a steric effect. The presence in the IR spectra of a very broad band of NH vibrations is a feature common to all of the amines (I, IV–VII) selected as the objects of investigation of these factors (except for the phenyl-substituted compound). The assumption of the existence of an interaction between the amino group and the double bond, i.e., that the conformation of the molecules of these amines promotes their cyclization, follows from this.

The results of cyclization of the first four amines (Table 2) indicate that steric shielding of the nitrogen atom by the substituent is compensated in the same order by an increase in the nucleophilicity of this atom. On the other hand, a decrease in the electron density on the nitrogen atom as a consequence of conjugation with the phenyl group suppresses the cyclization reaction; however, this effect is not a general one and is sometimes compensated by the conformational peculiarities of the molecule that promote its cyclization. In the case of a primary amine, cyclization proceeds satisfactorily only with mercuric acetate; this is explained by the high stability of the complex with mercuric chloride and the more electrophilic character of the acetate.

Substitution in the saturated portion of the amine molecule may change its conformation and thereby its ability to undergo cyclization. In addition, asymmetric induction is possible when a chiral center is

present in the molecule. On the other hand, if heterocyclization is an ionic reaction, complete or partial inversion of the polarization of the double bond may change the structure of the heterocycle formed. Finally, heterocylization of individual cis or trans isomers of ethyleneamines may make it possible to establish the direction of attack on the double bond by the nitrogen atom and the mercury cation.

The introduction of a methyl substituent into the side chain substantially changes the result of the reaction as compared with the unsubstituted compound. Thus, the heterocyclization of 2-propylamino-5-hexene (VIII) in the usual way gives two isomeric heterocycles with predominance of a pyrrolidine structure. Similar results were also obtained when a phenyl group was present in the α position (amine IX):

			Overall yield
VIII R=Pr, R'=Me;	66%	33%	60%
IX R=i-Pr, R'=Ph	80%	20%	80%
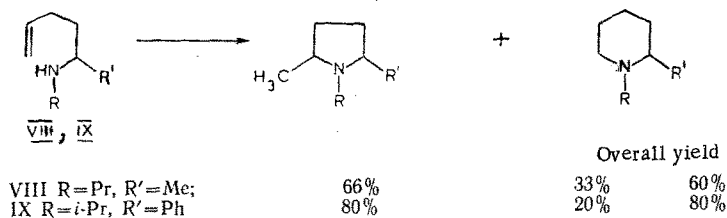
The PMR spectrum of the intermediate organomercury compound formed in the heterocyclization of amine VIII contains two doublets from a methyl group in the α position relative to the nitrogen atom. An asymmetric center in the α position relative to the nitrogen atom of the ethyleneamine thus induces the preferred formation of one of the diastereomeric forms of the organomercury compound (the ratio of stereoisomers is 75:25). However, the spectrum does not make it possible to choose between the pyrrolidine and piperidine structures, inasmuch as the utilization of the [199]Hg satellites for this purpose is impossible because of the strong multiplicity of the signal of the methylidyne proton.

The formation of five- and six-membered rings after the reduction of the intermediate organomercury compound both in the case of heterocyclization of amine VIII and in the case of heterocyclization of amine IX indicates that the presence of a substituent in the α position is sufficient to cause opening of the aziridinium ion via the two possible paths. It is possible that this is associated with asymmetric induction through the nitrogen atom in the case of α-substituted compounds. However, the confirmation of this assumption is extremely difficult, inasmuch as the appearance of a tertiary nitrogen atom per se introduces an additional chiral center, even when this sort of center is absent in the starting molecule.

Only the results of reduction made it possible to establish that the organomercury compound contains a five-membered ring. Inasmuch as it is an individual compound, one of the two reduction products is formed during rearrangement of the aziridinium ion. When the reduction conditions (temperature and reducing agent) were changed, the principal reaction product was always the five-membered ring, and it is precisely this fact that constitutes proof in favor of the pyrrolidine structure of the organomercury compound.

The intermediate of the reduction is two-ring aziridinium derivative X, despite the great strain in this system. Intermediates of this sort were isolated in the form of salts with anions of low nucleophilicity.
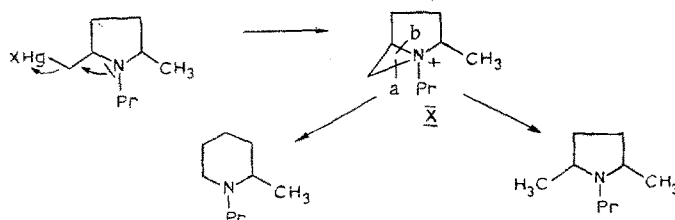

Thus the introduction of a substituent into the side chain on the whole changes the direction of the heterocyclization—reduction process. However, this sort of substitution is of significance for the second step (reduction) rather than for the first step (cyclization of the mercurinium ion) because of rearrangement of the intermediate aziridinium ion. The same intermediate can also be formed in the reduction of the organomercury compound obtained from 1-propylamino-4-pentene. The formation of only one reaction product in this case is explained either by a single direction of opening of the three-membered ring or by a high rate of reduction with bypassing of the step involving the aziridinium ion.

On turning to a discussion of the effect of substituents attached to the double bond of the ethyleneamine, one should assume that the formation of five- or six-membered rings will be determined by po-

larization of the double bond, the peculiarities of heterocyclization with the participation of an adjacent group (the possibility of steric drawing together of the double bond and the nitrogen atom of the side chain), and the strain in the resulting ring.

The heterocyclization of amine XI and subsequent reduction gave five-and six-membered rings with predominance of the former:
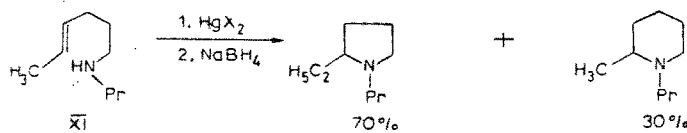

A study of the PMR spectrum of the intermediate organomercury compound indicates its individuality: Only one doublet is observed in the region of the resonance of methyl groups. It was possible to choose between structures XII and XIII by using the mercury satellite. In pyrrolidine XII the protons of the methyl group and the mercury atom are separated by three bonds, whereas they are separated by four bonds in piperidine XIII. A systematic investigation of the long range $J_{Hg,H}$ constants ($^4J \approx$ 15-45 Hz, ^2J and $^3J \approx$ 230-280 Hz) [15] made it possible to establish that in this case the organomercury compound has structure XII ($J_{Hg,CH_3} = 264$ Hz).
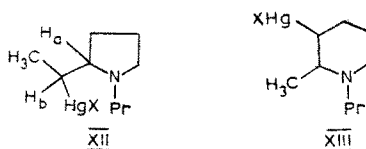
Thus, heterocyclization of the individual stereoisomer of the ethyleneamine gives only one diastereomer and is, consequently, a stereospecific reaction.

However, the formation of two heterocycles in the reduction of the organomercury compound is a consequence of the previously described rearrangement of the aziridinium ion.

The fact that different results — only one replacement of a methyl group with an ethyl group gave an individual product with a five-membered ring — were obtained with XIV is surprising. It is possible that the reduction of the intermediate aziridinium ion is extremely sensitive to the effect of substitution.
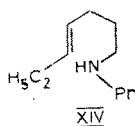

In contrast to what might have been expected from the point of view of polarization of the double bond, 1-amino-5-phenyl-4-pentene (XV) gives five-membered mercurated heterocycle XVI. In this case the geometry of the ring rather than polarization of the double bond evidently plays the decisive role; this is in agreement with the effect of anchimeric participation, which is responsible for the preferred formation of a five-membered ring. Reduction of the organomercury compound again results in the formation of two isomers:
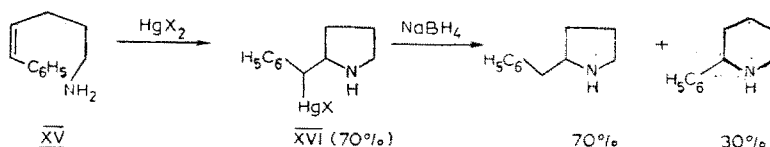

The reaction with ethyleneamine XVII, which is disubstituted at the end of the chain, proceeded via the following scheme:


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XXI
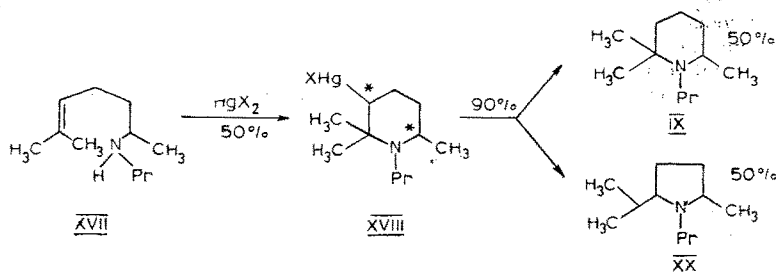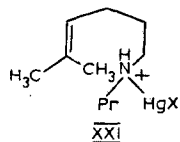
A study of the PMR spectrum of the reaction mixture (prior to reduction) indicates the presence of a complex (XXI) between the mercury salt and the starting amine and also organomercury compound XVIII. Demercuration by means of a hydride and by heating destroys the complex, leaving the individual organomercury compound. The fact that only one doublet of a methyl group of the organomercury compound, which should exist in two diastereomeric forms, is observed, whereas there are two doublets that are relatable to the complex, is interesting. Cyclization leads to two diastereomers, but in both cases the methyl group is oriented preferably equatorially because of interaction with the axial methyl substituent of the gem-dimethyl group. An equatorial orientation of the mercury-containing grouping is advantageous only to an insignificant degree.
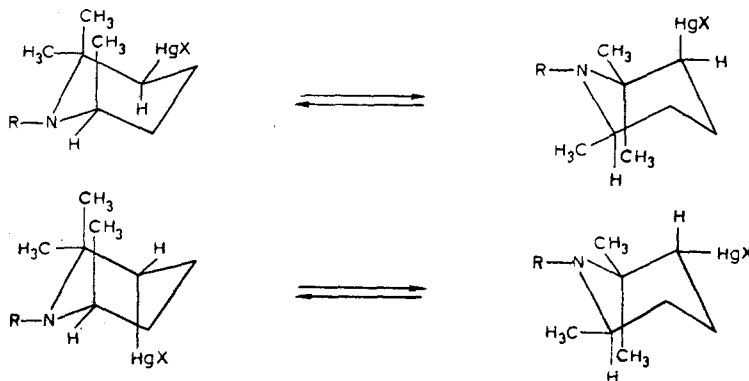
Complex XXI can exist in two diastereomeric forms, and the ammonium nitrogen atom is the second chiral center.

The assignment of a six-membered structure to the organomercury compound was based, on the one hand, on the absence of satellite signals of methyl groups, which should have been appreciable in the case of pyrrolidine XXII, and, on the other, on the relative excess of the piperidine isomer in the reduction products.
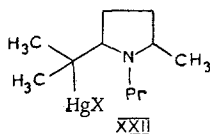
XXII

Compounds XXIII and XXIV were used to ascertain how a change in the length of the carbon chain of the ethyleneamine affects the direction of the reaction. In the first case heterocyclization could lead to the formation of a mercurated azetidine, and a seven-membered ring could result in the second case in the reduction step. However, it was found that the strain factor has greater significance in such systems than polarization of the double bond: Five- and six-membered rings, respectively, in individual form are obtained:
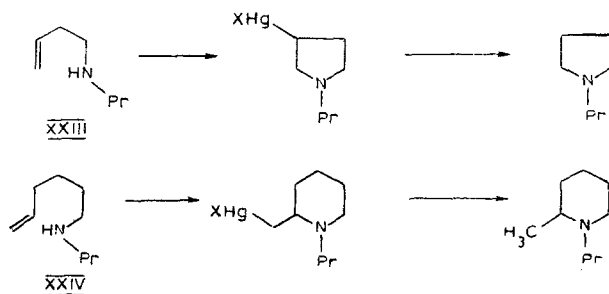
XXIII

XXIV

TABLE 3. Ratio of the Products of Cyclization of Amine XXVII

| Mercury salt	Solvent	XXVIII : XXIX ratio	Overall yield, %
Hg(OAc)₂	Pyridine	71 : 29	71
	Water	32 : 68	58
HgCl₂	Acetone	14 : 86	60
	Water	55 : 45	67

Stereochemistry of Intramolecular Aminomercuration

It is known that in hydroxymercuration reactions trans addition of the oxygen and mercury atoms occurs in most cases, except for bicyclic bridged systems, the strain of which causes cis addition. trans-Hydroxymercuration of cyclohexene was proved by means of x-ray diffraction [16], spectral, and optical methods. The reverse reaction also has the same stereochemistry: for example, the rate of dehydroxymercuration of trans 1-iodomercuri-2-methoxy-cyclohexane is 10 times that observed for the cis isomer.

However, in a review on the stereochemistry of hydroxymercuration [17] Zefirov showed that there are numerous exceptions to this rule, and he attempted to link the differences between the stereochemistry of different reactions with the fact that in some of them the mercury atom can coordinate with the heteroatom of the ethylene substrate, whereas in others it remains free. Thus, the stereochemistry of hydroxymercuration of 4-cyanocyclohexene is determined by coordination of the mercury atom with the cyano group, and this leads to a trans-addition product [18].
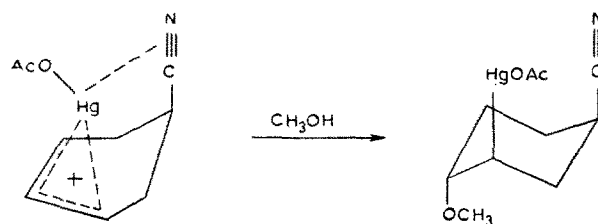
When coordination is absent, a cis product can be formed (reaction with carvomenthene). The hydroxymercuration of D-glucal is a cis-addition process, whereas the reaction with its triacetate, which apparently is capable of greater coordination with the mercury atom, gave a trans-addition product [19]. Considering the greater tendency of the mercury atom to form coordinate bonds with the nitrogen atom, it might have been assumed that the stereochemical peculiarities of the hydroxy- and aminomercuration reactions would be different. The transition state of the aminomercuration reaction, which corresponds to AdE₃ electrophilic addition [20], presumes the possibility of this sort of coordination:
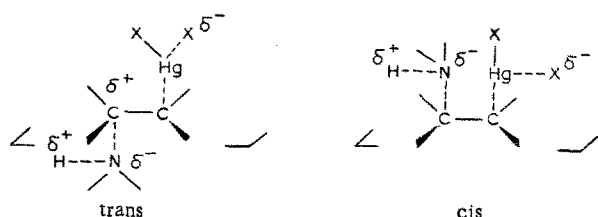
We attempted to establish the stereochemistry of aminomercuration with amines of the type shown below:
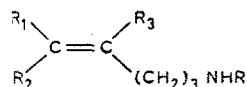
Organomercury compounds XXVa and XXVIa (in the case of a five-membered ring) or XXVb and XXVIb (in the case of a six-membered ring) should be obtained as a result of cis or trans addition.
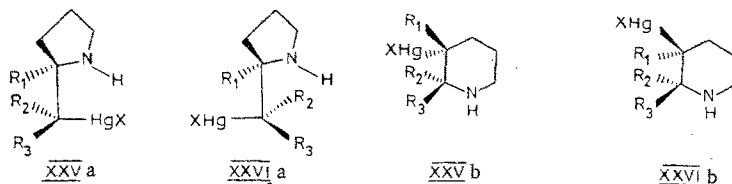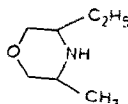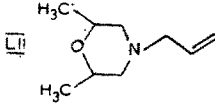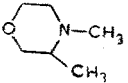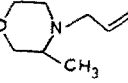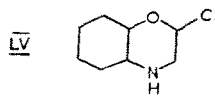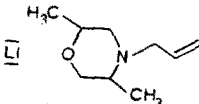

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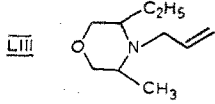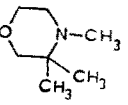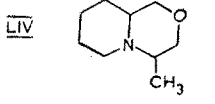
TABLE 4. Synthesis of Morpholine Derivatives by Means of Intramolecular Hydroxy- or Aminomercuration

Compound	Yield, % (method)	Compound	Yield, % (method)
XLVII	50 (a)	LII	45 (b)
XLVIII	36 (a)	LIII	46 (a)
XLIX	65 (a)	LIV	58 (a)
L	53 (a)	LV	50 (b)
LI	68 (a)		

When substrates having $R_1 = H$ and R_2 or $R_3 = H$ are used, the J_{HHg} spin—spin coupling constant can be related to the relative configuration at the two asymmetric carbon atoms and hence to the direction of attack on the double bond by the nitrogen and mercury atoms.

Amines IX, XIV, and XXVII were used as the ethylene substrate. As a result of heterocyclization of amine IX, which was assumed to have a trans configuration, individual organomercury compound XII was obtained; this proves the stereospecificity of the reaction. The J_{H,H_C} value was found to be 11 Hz for such systems.

Two organomercury compounds (XXVIII and XXIX) are obtained as a result of cyclization of o-(trans-2-buten-1-yl)-N-methylaniline (XXVII):
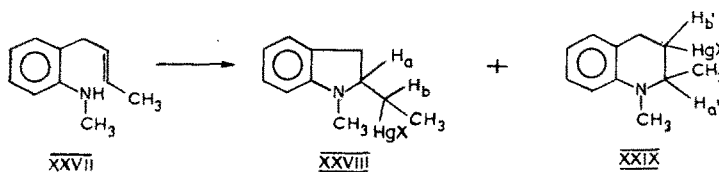
An analysis of the PMR spectrum in this case gave $J_{H_a,H_c} = 3$ Hz in the five-membered ring and $J_{H_{a'},H_{c'}} = 3$ Hz in the six-membered ring.

In order to establish the stereospecificity of aminomercuration, the spin—spin coupling constants must be compared with the calculated values.

The product of trans addition to amine IX will have configuration XXX, whereas the product of cis addition will have configuration XXXI:
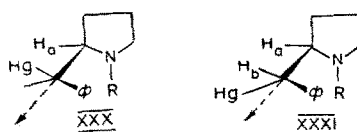
Both of these diastereomers can exist in the form of three skew conformers XXXa-c and XXXIa-c, respectively:

XXX a   XXX b   XXX c

XXXI a   XXXI b   XXXI c
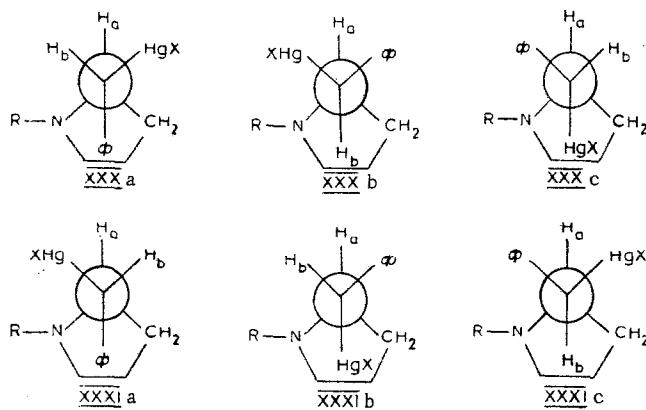
The spin−spin coupling constants will then be determined by the expressions

$$J_{tc} = x_a J \text{gauche} + x_b J \text{ anti } + x_c J \text{ gauche },$$

$$J_{cc} = x_a J \text{gauche} + x_b J \text{gauche} + x_c J \text{ anti },$$

where J_{tc} and J_{cc} are the constants of trans and cis addition to the cis amine, and $x_a \ldots x_c$ are the populations of each conformer. Because of the strong attraction between the nitrogen and mercury atoms the populations of the conformers should be extremely different, and the conformational equilibrium will be shifted to favor XXXb,c and XXXIa,b. In addition, if one takes into account repulsion between the phenyl group and the nitrogen atom, the population of conformer XXXc will decrease in favor of XXXb, as a result of which $J_{tc} \geq \frac{1}{2}(J^{anti} + J^{gauche})$. Hence $J_{tc} = \frac{1}{2}(J^{anti} + J^{gauche})$ and $J_{cc} = J^{gauche}$. Thus, trans addition leads preferably to conformer XXXb in which two hydrogen atoms are in the anti position, whereas cis addition leads to two conformers XXXIa,b (with predominance of XXXIb) in which these two hydrogen atoms are in the gauche position. The application of the Karplus equation makes it possible to estimate $J^{gauche} = 4 \pm 1$ Hz and $J^{anti} = 10.5 \pm 1.5$ Hz. Then, $J_{tc} = 7.2 \pm 1.2$ Hz and $J_{cc} = 4 \pm 1$ Hz. The experimental J value of 11 Hz for the product of heterocyclization of cis–amine XIV indicates that trans addition of the mercury and nitrogen atoms occurs.

A similar interpretation of the results can also be given in the case of heterocyclization of trans-amine XXVII:

XXVII   XXXII   XXXIII

XXXII a   XXXII b   XXXII c

XXXIII a   XXXIII b   XXXIII c
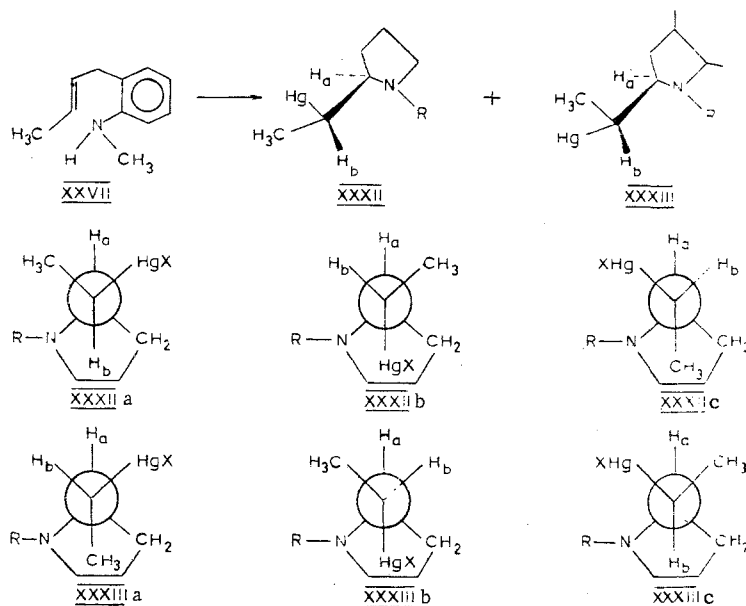
Assuming equal populations of the XXXIIb,c and XXXIIIb,c conformations, we obtained $J_{tt} = J^{gauche} = 4 \pm 1$ Hz and $J_{ct} = 7.2 \pm 2.5$ Hz. The experimental J value (3 Hz) again confirms that the reaction is trans addition.

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Thus aminomercuration is a regiospecific and stereospecific reaction, but the reduction step is not regiospecific because of the intermediate formation of an aziridinium ion.

Some Special Examples of Heterocyclization
## of Ethyleneamines

The reaction with amine XXVII gave two organomercury compounds (the only such case in the investigated series) — indoline derivative XXVIII and tetrahydroquinoline derivative XXIX in an overall yield of 70%. The presence of two isomers is confirmed by the $^3J_{Hg,CH_3}$ value of 272 Hz and the $^4J_{Hg,CH_3}$ value of 19 Hz. Their ratio depends on the anion of the mercury salt and the solvent (Table 3).

The indoline : tetrahydroquinoline ratio changed only slightly in the reduction step.

Strained system XXXIV underwent heterocyclization very easily to give only one organomercury compound (XXXV). A comparison of $J_{Hg,6-H} = 264$ Hz with the analogous value for XXXVI (88 Hz) shows that trans addition occurs in this case also.
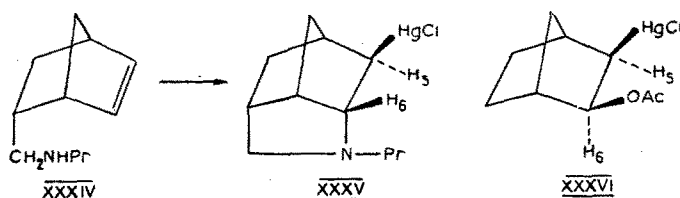

The formation of two types of heterocycles is possible in the heterocyclization of amines containing an endocyclic double bond:
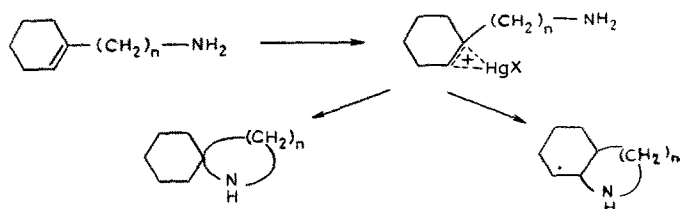

Cyclization of amines with n = 3 and 4 is specific and gives only the spiroheterocycle:

| Amine	R	n	Yield, %
XXXVII	H	3	40
XXXVIII	H	4	48
XXXIX	t-C$_4$H$_9$	3	58
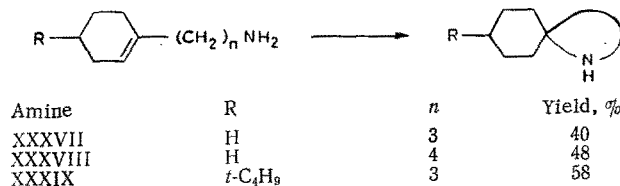
In the case of amine XXXIX two stereoisomers (XL and XLI) are formed with predominance of the isomer with the nitrogen atom in the axial position:
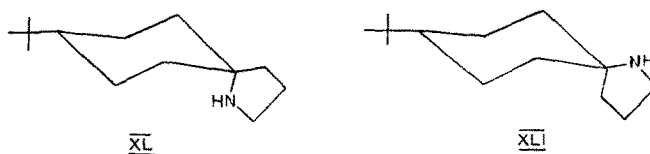
Octahydroindole XLIII is obtained rather than the spiroazetidine as a result of heterocyclization of amine XLII, inasmuch as a strained system arises in the case of the spiro compound.
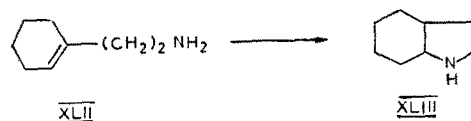

Reaction with amine XLIV and subsequent reduction give two heterocycles:

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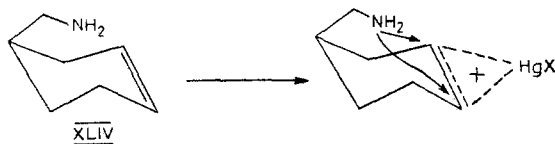
We studied the possibility of using the same method to obtain heterocycles with two heteroatoms — morpholines and piperazines. We established that a related method for the synthesis of the heterocycles by intramolecular hydroxymercuration is limited in character.

Morpholines are formed by the action of mercuric acetate under the conditions of intramolecular aminomercuration of allyl ethers XLV or hydroxymercuration of 2-(allylamino)ethanols XLVI:
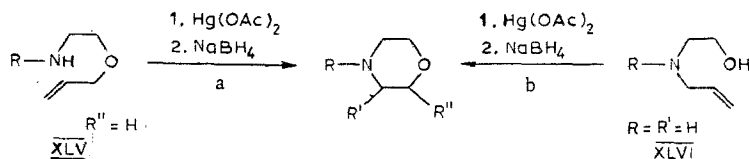
Heterocyclization by aminomercuration was carried out by means of mercuric acetate in aqueous THF (1:1). The intermediate organomercury compound was reduced with sodium borohydride in alkaline media.

In contrast to aminomercuration (method a), hydroxymercuration of allylamino alcohols (method b) is not a general method for the preparation of morpholines and gives satisfactory results only with amino alcohols having a tertiary amino group or with amino alcohols whose conformations are favorable for cyclization (LV) (Table 4).

The primary formation of one of the diastereomers was observed in all cases when there were two chiral centers in the resulting morpholine. Thus, their ratio in the case of LI was 80:20. The shift of the signals of the protons of the CH_3 groups in the PMR spectra as a result of complexing with the lanthanides corresponds to the literature data for an equatorial orientation of these groups. When these substituents are present in the 3 and 5 positions (LIII and LIV), they have a cis orientation, but when they are present in the 2 and 5 positions they have a trans orientation (LI). This may be explained by allowance for the 1,3-diaxial interactions during the formation of the rings.

All attempts to obtain 2-methylpiperazines by intramolecular aminomercuration of N-allylethylene-diamines (method a) were unsuccessful, undoubtedly because of the formation of a complex between the mercury salt and the two nitrogen atoms.

Competition between Hydroxy- and Aminomercuration

· As we have already pointed out, as a result of anchimeric acceleration intramolecular aminomercuration is realized considerably more easily than intermolecular aminomercuration. It was also established that in the case of intermolecular processes the rate of hydroxymercuration is substantially higher than the rate of aminomercuration. The explanation for this consists in the stability of the complex formed between the amine and the mercury salt; this partially blocks the ionization of the latter. On the other hand, in the case of heterocyclization, aminomercuration of an ethylene substrate takes place in a few minutes, whereas hydroxymercuration of an ethylene alcohol is complete only after several hours.

We first of all attempted to establish the possibility of competition between inter- and intramolecular aminomercuration in those cases in which the conditions are less favorable for the latter. The mercuration of allylamine by means of mercuric acetate (a three-membered ring should be obtained here during intramolecular reaction) gave cis- and trans-2,5-dimethylpiperazines (which can be explained by both intermolecular and intramolecular processes) and allylacetamide.

We next examined the intermolecular aminomercuration of diallylamines:
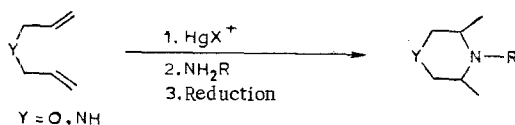
This sort of reaction is, in principle, possible, as demonstrated in the case of allyl ethers [5]. However, all experiments with diallylamine gave only its acetamide (X = CH₃COO).

Finally, we accomplished the intramolecular heterocyclization of ethylene amino alcohols LVI and LVII. In the first case, the amino and hydroxy groups are identically sterically accessible, whereas in the second case drawing together of the double bond and the amino group is less favorable than drawing together with the hydroxyl group.
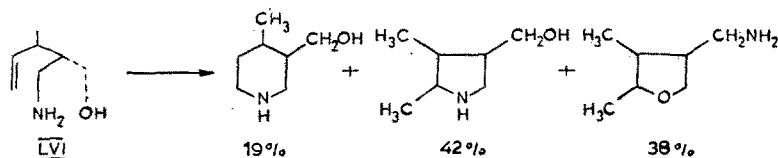
Thus, amino alcohol LVI gives 61% of aminomercuration products and only 38% of hydroxymercuration products; when allowance is made for the high nucleophilicity of the nitrogen atom, this confirms a mechanism with participation of a neighboring group.

At the same time, amino alcohol LVII gives only a hydroxymercuration product:
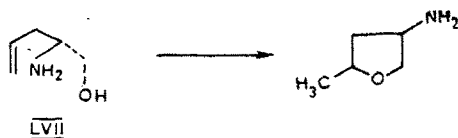
Consequently, although intramolecular aminomercuration competes successfully with hydroxymercuration in the case of identically favorable geometrical characteristics, it nevertheless remains extremely sensitive to them.

The presence of two functional groups in both of the latter models makes it possible to hope for further development of aminomercuration reactions that lead to functionally substituted heterocycles.

In conclusion, we used the results obtained above for the cyclization of a system with two double bonds, which made it possible to carry out amino- and hydroxymercuration simultaneously:
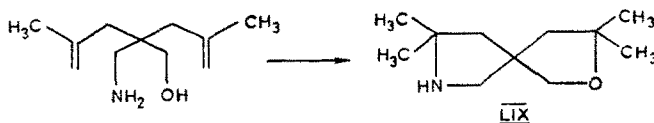
The formation of spiran LIX is an interesting example of the extension of heterocyclization to all substrates containing amino and hydroxy groups as well as several double bonds.

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