SYNTHESIS OF DERIVATIVES OF TETRAHYDROFURAN AND TETRAHYDROPYRAN BY INTRAMOLECULAR CYCLIZATION OF UNSATURATED HYDROXY COMPOUNDS (REVIEW)

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The literature data on reactions involving electrophilic heterocyclization of δ,ε-unsaturated alcohols, 2-allylphenols, oxiranes, aldehydes, and ketones are correlated. The factors that affects the reactivities of the unsaturated compounds (the structure of the substrate, the nature of the electrophile, and the nature of the solvent) in intramolecular cyclization are discussed. The problems of the regioselectivity of the addition and the stereochemistry of the resulting cyclization products are examined, and kinetic data are presented.

After the publication of a review on addition reactions involving intramolecular ring formation [1], a large number of studies have been published in this area, and it has now become necessary to deal with not only individual examples of the use of this reaction for the synthesis of one or another class of heterocycles but also with the question of how general this method of synthesis of various heterocycles is.

A review [2] on the electrophilic heterocyclization of unsaturated amines under the influence of mercury salts, which leads to the formation of five- and six-membered nitrogen-containing heterocycles, was published in 1975.

In the present review we examined the electrophilic heterocyclization of δ,ε-unsaturated alcohols, oxiranes, ketones, and o-allylphenols, which leads to derivatives of tetrahydrofuran, octahydrobenzofuran, tetrahydropyran, dihydrofuran, and benzofuran. The factors that affect the reactivities of the unsaturated compounds (the structure of the substrate, the nature of the electrophilic agent, and the nature of the solvent) and the regioselectivity of the addition to them of various electrophiles are discussed, the stereochemistry of the resulting cyclic products is examined, and kinetic data primarily on reactions involving the iodocyclization of unsaturated hydroxy compounds are presented. Studies in these areas that have been published in recent years are included in the review. However, of necessity, some earlier studies are also presented.

In connection with the voluminous literature data on the intramolecular cyclization of unsaturated hydroxy compounds under the influence of a proton, these reactions are not discussed in this review. They deserve to be examined in a separate publication. For the same reason, studies dealing with the preparation of oxygen-containing heterocycles by heterocyclization of 1,4- and 1,5-dienes are not included in this review.

1. Factors That Determine the Reactivities and Regioselectivities of the Intramolecular Cyclization of Unsaturated Hydroxy Compounds

Sane and Singer described the addition of mercury salts of δ,ε-unsaturated alcohols for the first time in 1902 [3]. Depending on the structure of the starting alcohols, they obtained derivatives of tetrahydrofurans or tetrahydropyrans. The mercuricyclization of pent-4-en-1-ol, hex-5-en-1-ol, and hex-5-en-2-ol [4, 5], 2,2-diphenylpent-4-en-1-ol [6], and terpineol [3, 7] to the corresponding tetrahydrofuran derivatives was subsequently studied. The reaction of o-allylphenols with mercury and thallium salts [8-16], iodine and iodine monochloride [17-21], and benzenesulfenyl chloride and N-phenylselenylphthal(succin)imides [22, 23] leads to dihydrobenzofurans.

Products of "simple" and "mixed" addition to the double bond are often obtained, in addition to cyclic products, as a result of the addition of electrophiles of δ,ε-unsaturated alcohols.

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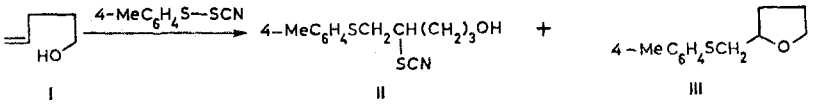
The yields of cyclic products often depend, other things being equal, on the nature of the electrophilic agent. Halogens, iodine monochloride, cyanogen iodide, mercury and thallium salts, arenesulfenyl(selenyl) halides and cyanides, N-iodo(bromo)succinamides, etc., are used as the electrophiles.

Mercury salts and iodine react with unsaturated oxygen-containing compounds to give primary cyclic products. The reactions with other electrophiles proceed less selectively.

Mixtures of cyclic (50-60% when n = 3, 5-10% when n = 4) and noncyclic products of addition to the double bond are obtained in the bromination of $CH_2=CH(CH_2)_nOH$ (n = 1-4) [24]. A similar pattern is observed in the bromination of α- and β-alkyl-substituted pent-4-en-1-ols [25]. The iodination of pent-4-en-1-ol and hex-5-en-1-ol leads to the formation of only cyclic products. Thus the addition of iodine nitrate in chloroform–pyridine to pent-4-en-1-ol and hex-5-en-1-ol [26, 27] gives, respectively, 2-iodomethyl-tetrahydrofuran (60%) and 2-iodomethyltetrahydropyran (17%), whereas a benzofuran derivative is formed in 33% yield in the case of 2-allylphenol, while iodine in aqueous KI solutions reacts with these compounds to give cyclic products in quantitative yields [18, 21, 28, 29].

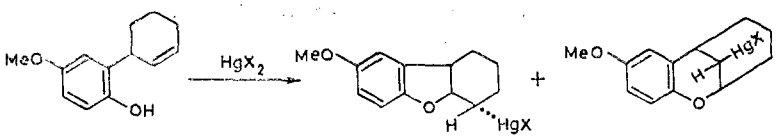
Similarly, noncyclic addition product II (80%) and only 10% of tetrahydrofuran derivative III are obtained in the reaction of pent-4-ene-1-ol (I) with benzenesulfenyl thiocyanate [30] in anhydrous CH_3COOH, whereas the ratio of the reaction products is reversed in the reaction of these components in the presence of $LiClO_4$.



I II III

The analogous reaction of pent-4-en-1-ol with benzeneselenyl chloride and N-phenylselenophthal(succin)imides [22, 23, 31] leads to 2-phenylselenomethyltetrahydrofuran in 75-95% yield.

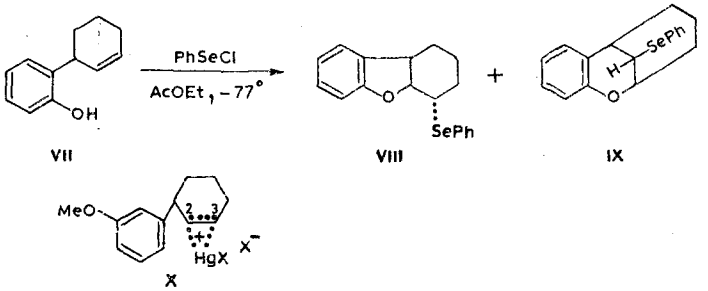
In the cases in which the production of five- and six-membered heterocycles is possible the nature of the electrophilic agent affects not only the ratios of the resulting cyclic and noncyclic products but also affects the size of the resulting ring. Thus the mercuricyclization of 2-(cyclohexen-2-yl)-4-methoxyphenol (IV) with $Hg(OAc)_2$ [32] leads only to 4-acetoxymercuro-1,2,3,4,4a,9b-hexahydro-8-methoxydibenzofuran (V). A mixture of V and VI in ratios of 56:44 and 24:76, respectively, is obtained by the action of $Hg(OCOCH_2Cl)_2$ and $Hg(OCOCHCl_2)_2$ on phenol IV, whereas all the remaining electrophiles lead to the formation of chromans VI. A mixture of benzofuran VIII and chroman IX in a ratio of 3:1 was also obtained in 67% yield in the reaction of cyclohexenylphenol VII with benzeneselenyl chloride [22, 33].



IV V VI

X = OAc, Cl, NO_3, ClO_4, $OCOCH_2Cl$, $OCOCHCl_2$, $OCOCCl_3$, $OCOCF_3$

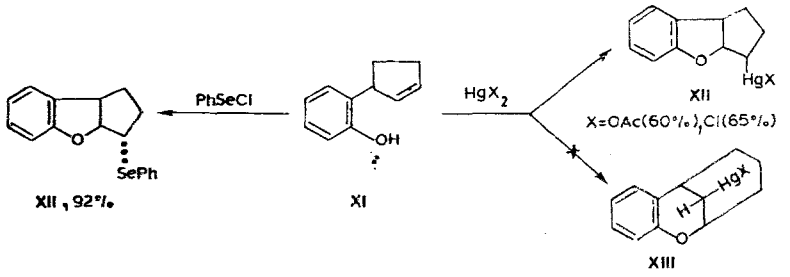
The regioselectivity of the mercuricyclization of phenol IV depends on the electronic nature of the anionic ligand in HgX_2. More highly electronegative ligands lead to chroman VI [32]. These differences in the direction of the reaction can evidently be associated with the distribution of the electron density between the C_2 and C_3 atoms in complex X.



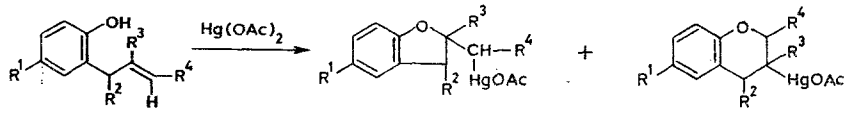
VII VIII IX

X

In the heterocyclization of 2-(cyclopenten-2-yl)phenol (XI) the direction of the reaction is determined by the thermodynamic factor. Of the two possible structures [benzofuran (XII) and chroman (XIII)], only the less strained benzofuran structure is formed in mercuration [32] and benzeneselenylchlorination [22]



In addition to the nature of the electrophilic agent, the structure of the starting unsaturated compound has a significant effect on the size of the resulting ring. The presence of a methyl group attached to the terminal carbon atom of the double bond of 2-allylphenols (XIVf,g) in the case of acetoxymercuration [34] leads to the formation of a mixture of substituted benzofurans XVf,g and benzopyrans XVIf,g in a ratio of ~1:1, whereas compounds in which a methyl group is absent give benzofuran derivatives in quantitative yields.



XIV XV XVI

XIV–XVI a $R^1=R^2=R^3=R^4=H$; b $R^1=CH_3$, $R^2=R^3=R^4=H$; c $R^2=CH_3$, $R^1=R^3=R^4=H$;
d $R^1=R^2=CH_3$, $R^3=R^4=H$; e $R^3=CH_3$, $R^1=R^2=R^4=H$; f $R^4=CH_3$, $R^1=R^2=R^3=H$;
g $R^1=R^4=CH_3$, $R^2=R^3=H$; h $R^2=C_6H_5$, $R^1=R^3=R^4=H$

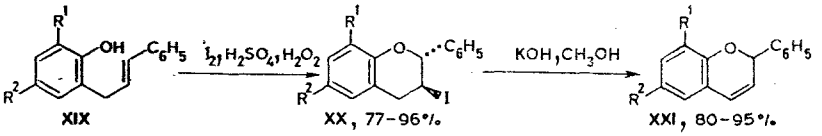
The composition of the products changes only slightly when this reaction is carried out in water, pyridine, and aqueous tetrahydrofuran [34].

The presence of two methyl groups attached to the terminal carbon atom of the double bond of XVII in their reaction with N-iodosuccinimide [35] leads primarily to chroman derivatives XVIII:

X=6-CH_3 (90%); 7-OCH_3 (67%)

Under similar conditions 2-cinnamyl-4-methylphenol with N-iodosuccinimide gives 3-iodo-6-methylflavan, which is converted to 6-methyl-2H-flavene in 90% yield when it is treated with an alcohol solution of alkali [35].

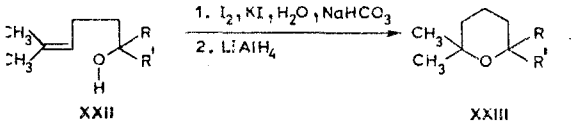
The heterocyclization of 2-cinnamylphenols (XIX) [36] with an alcohol solution of iodine in the presence of H_2SO_4 and H_2O_2 leads to 3-iodoflavans (XX); the latter are converted to 2H-flavenes XXI by splitting out hydrogen iodide. A trans configuration was assigned to the 3-iodoflavans on the basis of the PMR spectra.



XIX–XXI a $R^1=R^2=t\text{-}C_4H_9$; b $R^1=t\text{-}C_4H_9$, $R^2=H$; c $R^1=CH_3$, $R^2=t\text{-}C_4H_9$;
d $R^1=s\text{-}C_4H_9$, $R^2=H$; e $R^1=C_2H_5$, $R^2=H$; f $R^1=CH_3$, $R^2=H$

In a study of the iodocyclization [37–40] and mercuricyclization [41–43] of unsaturated alcohols XXII and XXXII it was found that only tetrahydrofuran derivatives XXXIII are formed

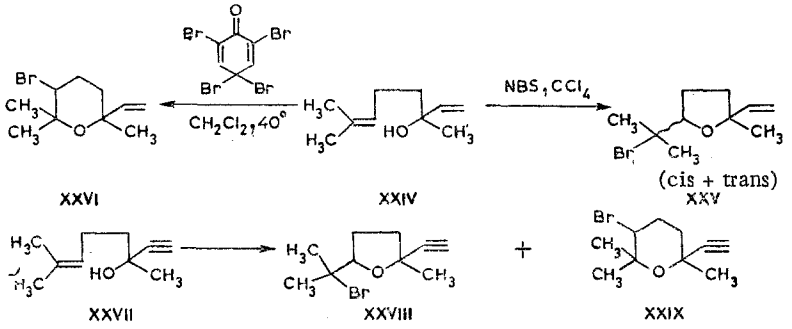
from alcohols XXXII, while alcohols XXII, in which two methyl groups are attached to the terminal carbon atom of the double bond, give tetrahydropyran derivatives (XXIII):



XXII XXIII

XXII-XXIII a $R=CH_3$, $R'=H$; b $R=C_6H_5$, $R'=H$; c $R=CH_3$, $R'=C_2H_5$

It is interesting that the presence of two methyl groups attached to the terminal carbon atom of the double bond of 3,7-dimethylocta-1,6-dien-3-ol (XXIV), when it is treated with N-bromosuccinimide, gives a mixture of stereoisomeric tetrahydrofurans XXV, whereas the reaction of XXIV with 2,4,4,6-tetrabromocyclohexadienone [45] leads only to tetrahydropyran XXVI. The primary formation of six-membered heteroring XXIX is also observed in the reaction of 3,7-dimethyloct-1-yn-6-en-3-ol (XXVII) with tetrabromocyclohexadienone. The XXVIII:XXIX ratio is 1:4. The reaction of alcohol XXVII with N-bromosuccinimide gives primarily tetrahydropyran XXIX.



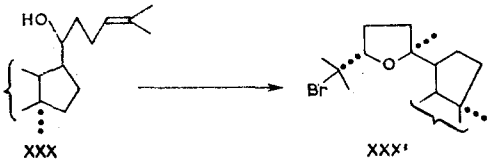
XXVI XXIV XXV

XXVII XXVIII XXIX

Thus it follows from the experimental data presented above that several factors affect the size of the resulting ring in the electrophilic heterocyclization of unsaturated alcohols. Of these, the determining factor is the nature of the electrophilic agent.

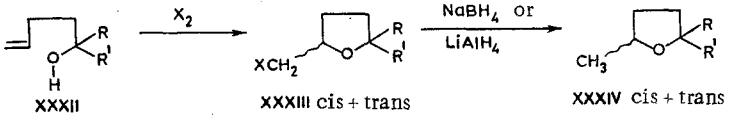
2. Stereochemistry of the Products of Intramolecular Heterocyclozation of δ,ε-Unsaturated Alcohols

It follows from the data presented below that the electrophilic heterocyclization of unsaturated alcohols proceeds via a trans-addition scheme. The trans stereospecificity in reactions involving electrophilic heterocyclization of unsaturated alcohols was demonstrated for the first time in the bromination of triperpenes of the damarane series (XXX) with N-bromosuccinimide [46], as a result of which only the trans isomer of tetrahydrofuran XXXI was obtained:



XXX XXX'

Data on the mercuricyclization [41, 47] and iodocyclization [37] of alcohols XXXII are presented in the scheme and in Table 1:



XXXII XXXIII cis + trans XXXIV cis + trans

$X_2 = HgCl_2, Hg(OAc)_2, I_2$ a $R=CH_3$, $R'=H$; b $R=t\text{-}C_4H_9$, $R'=H$; c $R=C_6H_5$, $R'=H$; d $R=CH_3$, $R'=C_2H_5$

It is apparent from Table 1 that the ratios of the tetrahydrofuran isomers depend primarily on the nature of the electrophile and the reaction conditions.

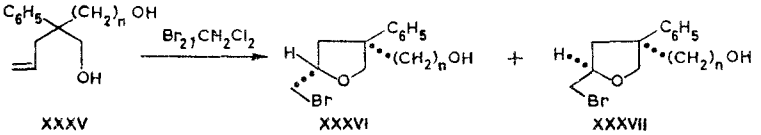
TABLE 1. Compositions of the Mixtures of Diastereomeric Tetrahydrofurans XXXIII and XXXIV*

Compound	R	R'	Chloromercuration		Acetoxymercuration		Iodination	
			cis, %	trans, %	cis, %	trans, %	cis, %	trans, %
XXXIIIa	CH_3	H	58	42	55 (67)	45 (33)	30 (33)	70 (67)
XXXIIIb	C_4H_9	H	64	36	24 (22)	76 (78)	— —	— —
XXXIIIc	C_6H_5	H	93 (90)	7 (10)	48 (47)	52 (53)	— (64)	— (36)
XXXIIId	CH_3	C_2H_5	—	—	—	—	55 —	45 —

*The percentages of the isomers in reduction products XXXIVa-d are given in parentheses.

The primary formation of cis isomers in the chloromercuration and iodination of alcohol XXXIIc can be explained by the effect of vertical stabilization [48] of the phenyl group of the transition state of ring formation.

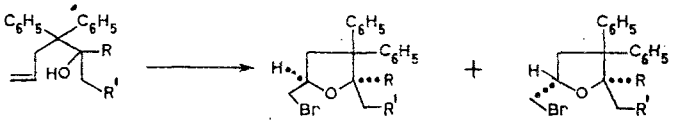
An interesting result was obtained in the bromination of unsaturated alcohols that are substituted in the α and β positions relative to the OH group [49]. The stereoselective formation of trans-2,4-substituted tetrahydrofurans XXXVI and XXVIII is observed in the bromocyclization of 2-phenyl-2-hydroxymethylpent-4-en-1-ol (XXXVa). The ratio of the cis and trans isomers is 2:1. The stereoselectivity of the reaction is lost in the case of alcohol XXXVb:



XXXV XXXVI XXXVII

a $n=1$; b $n=2$

The absence of stereoselectivity is also observed in the bromination of amino alcohol XXXVIIIa, whereas its analogs XXXVIIIb and XXXVIIIc give only cis-tetrahydrofurans XXXIXb and XXXIXc upon bromocyclization.

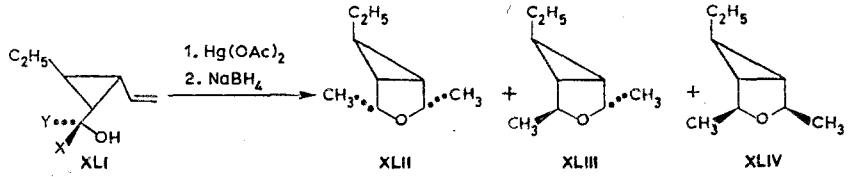


XXXVIII XXXIX, cis XL, trans

XXXVIII–XL a R=CH_3, R'=$NHCH_3$; b R=H, R'=Cl; c R=H, R'=$NHCH_3$

The stereochemical result of bromination of the alcohols mentioned above depends on the effect of the α and β substituents on the ease of formation of the cyclic transition state.

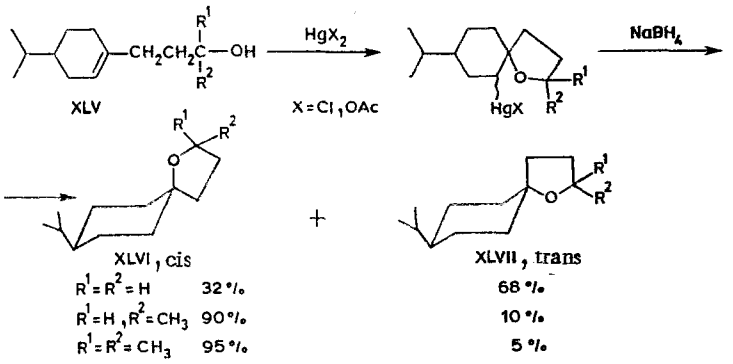
Acetoxymercuration of diastereomeric 1-(2-ethyl-3-vinylcyclopropyl)ethanols XLIa,b [50] and subsequent reduction of the products with $NaBH_4$ lead to mixtures of di-endo-(XLII), eso, endo-(XLIII), and di-exo-(XLIV)-2,4-dimethyl-6-ethyl-3-oxabicyclo[3.1.$0^{1,5}$]hexanes. Alcohol XLIa gives a mixture of XLIII and XLIV in a ratio of 1:3, while XLIb gives a mixture of XLII and XLIII (1:6).



XLI XLII XLIII XLIV

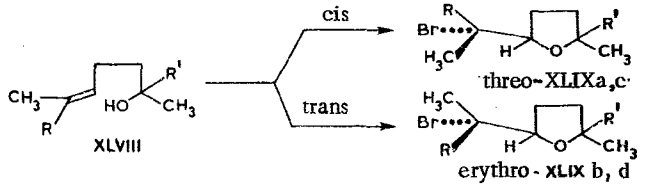
XLI a X=CH_3, Y=H; b X=H, Y=CH_3

In the case of mercuricyclization of alcohols XLV [51] the size of the R^1 and R^2 substituents affects the yields of the cis and trans isomers of tetrahydrofurans XLVI and XLVII:



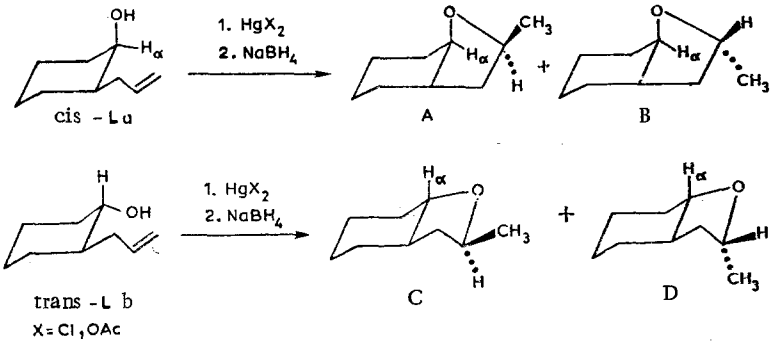
The primary formation of cis isomers XLVI when the number of methyl groups in the α position relative to the OH group of XLV is increased is evidently associated with the significant steric hindrance to realization of the trans-addition scheme.

The brominzation [44, 52] of cis- and trans-2,6,10-trimethylundec-5-en-2-ols (XLVIIIa,b) with N-bromosuccinimide gives, respectively, threo- and erythro-2,2-dimethyl-5-(2-bromo-6-methyl-2-heptyl)tetrahydrofurans (XLIXa,b), whereas the isomeric 3,7,11-trimethyldodeca-1,6,10-trien-3-ols (XLVIIIc,d) give mixtures of the cis and trans forms of erythro- and threo-2-methyl-2-vinyl-5-(2-bromo-6-methylhept-2-en-2-yl)tetrahydrofurans (XLIXc,d).



XLVIII, XLIX a $R=(CH_2)_3CH(CH_3)_2$, $R'=CH_3$, cis; b $R=(CH_2)_3CH(CH_3)_2$, $R'=CH_3$, trans; c $R=(CH_2)_3CH=C(CH_3)_2$, $R'=CH=CH_2$, cis; d $R=(CH_2)_3CH=C(CH_3)_2$, $R'=CH=CH_2$, trans

The mercuration of cis- and trans-2-allylcyclohexanes (La,b) [53] leads to 2-chloro(acetoxy)mercurimethyloctahydrobenzofurans, which upon reduction with $NaBH_4$ give stereoisomeric 2-methyloctahydrobenzofurans A-D.



The mercuricyclization of cyclohexanols La,b is characterized by a certain degree of stereoselectivity. The stereoselectivity of the acetoxymercuration of substituted 2-allylphenols is also slight [34].

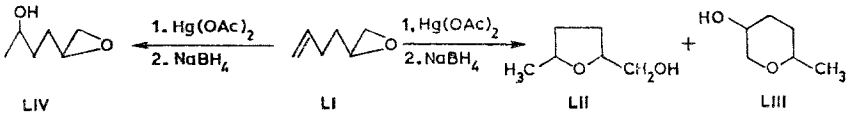
Thus the stereochemical result of the electrophilic heterocyclization of unsaturated alcohols and phenols depends on the nature of the electrophilic agent, the structure of the substrate, and the reaction conditions.

3. Participation of Epoxide and Carbonyl Groups of Unsaturated Compounds in Electrophilic Heterocyclization Reactions

The formation of tetrahydrofuran and tetrahydropyran derivatives as a result of the electrophilic heterocyclization of unsaturated oxiranes is possible both in the case of direct participation of the oxygen atom of the oxirane ring and in the case of the participation of

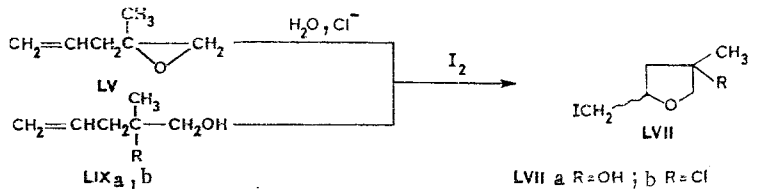
the hydroxy group of the unsaturated glycols that are formed by opening of the oxirane ring in water. When electrophiles that are capable of adding rapidly to the double bond of unsaturated oxiranes are used, the reaction may proceed through the intermediate formation of an adduct of the electrophile at the double bond.

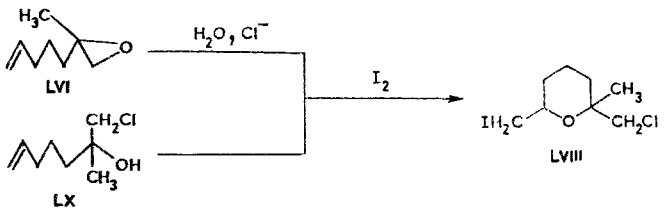
The direct participation of the oxirane ring in heterocyclization is observed in the acetoxymercuration of 1,5-hexadiene oxide (LI) [54], as a result of which a mixture of derivatives of tetrahydrofuran (LII) and tetrahydropyran (LIII) is obtained. This conclusion was drawn on the basis of the fact that the rate of mercuration of the unsaturated glycol that was obtained separately by hydrolysis of oxide LI is higher by a factor of three than the rate of acetoxymercuration of the oxide itself. In addition, the formation of an adduct of mercuric acetate (LIV) at the double bond of 1,5-hexadiene oxide is not observed as a result of the reaction of oxide LI with $Hg(OAc)_2$.



A similar scheme has been proposed for the iodocyclization of the nitrile and methyl ester of (β,β-dimethylbutene-1-yl)glycidic acid [55]. In this reaction the rate of iodination of the unsaturated alcohol obtained in the hydrolysis of the glycidic ester is higher by a factor of 12 than in the case of the latter [56].

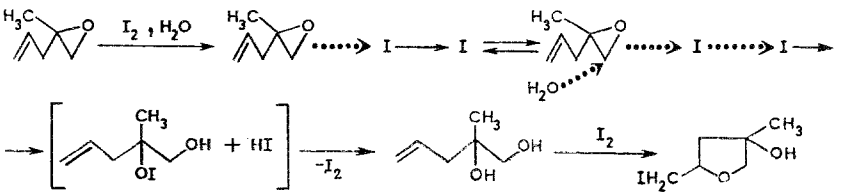
Electrophilic heterocyclization of unsaturated oxiranes, which includes the intermediate formation of alcohols due to opening of the oxirane ring under the influence of water or I^- and Cl^- anions, is realized in the iodocyclization of 1,2-epoxy-2-methylpent-4-ene (LV) and 1,2-epoxy-2-methylhept-6-ene (LVI). Tetrahydrofuran (LVII) and tetrahydropyran (LVIII) derivatives, respectively, were obtained in the iodination of these compounds [57].



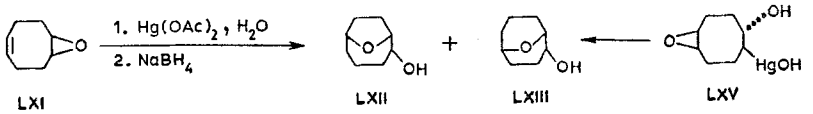


The proposed scheme is confirmed by the fact that the rate constants for the iodination of both oxirane LV and the products of opening of the oxide ring LIXa,b are 1.81 ± 0.12 liters/mole-sec at 30°C. A similar pattern is also observed in the iodocyclization of oxirane VLI and its hydrolysis product LX [58].

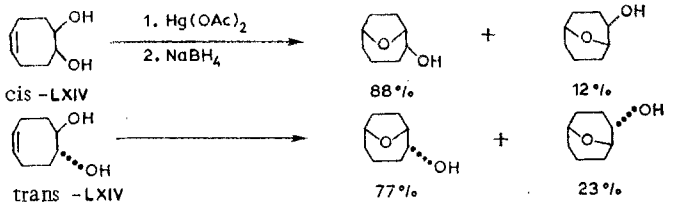
From these data, the iodocyclization of unsaturated oxiranes LV and LVI can be represented by the scheme



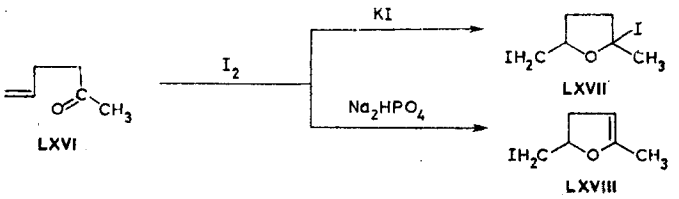
Jernow and co-workers [54] and Ganter and Zwahlen [59] obtained a mixture of 2-hydroxy-9-oxabicyclo[4.2.1]nonane (LXII) and 2-hydroxy-9-oxabicyclo[3.3.1]nonane (LXIII) in a ratio of 1:3 in the acetoxymercuration of 1,5-cyclooctadiene monoxide (LXI).



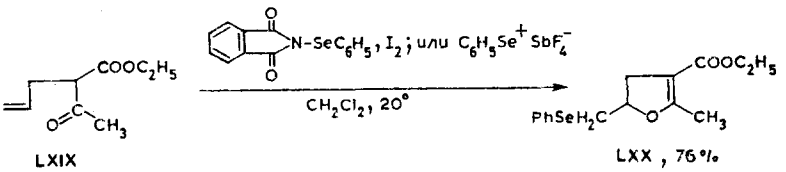
It has been shown [54] that cis- and trans-1-cyclooctene-5,6-diols (LXIV), which could have been obtained in the hydrolysis of oxide LXI, give a mixture of 2-hydroxy-9-oxabicyclo-[4.2.1]- and 2-hydroxy-9-oxabicyclo[3.3.1]nonanes in a ratio of 7:1 in the case of the cis diol and a ratio of 3:1 in the case of the trans diol in the acetoxymercuration of a mixture of 2-hydroxy-9-oxabicyclo[4.2.1]- and 2-hydroxy-9-oxabicyclo[3.3.1]nonanes. It is apparent that the ratio of the cyclic products obtained in the acetoxymercuration of the diols differs from the ratio in the case of the acetoxymercuration of 1,5-cyclooctadiene oxide. The product of the addition of mercuric acetate to the double bond of 1,5-cyclooctadiene oxide (LXV) is readily converted to a mixture of cyclic products LXII and LXIII in a ratio that is the same as in the acetoxymercuration of 1,5-cyclooctadiene oxide. On the basis of this, it was concluded that the acetoxymercuration of 1,5-cyclooctadiene oxide proceeds through the intermediate formation of an adduct of mercury at the double bond of 1,5-cyclooctadiene oxide



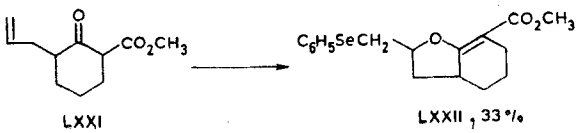
In addition to the enumerated functional groups, the oxygen atom of the carbonyl group of γ,δ-unsaturated ketones and aldehydes participates in electrophilic heterocyclization reactions. Thus derivatives of either tetrahydrofuran (LXVII) or dihydrofuran (LXVIII) are obtained in the iodination [60] of allylacetone (LXVI) and 2-allylcyclohexanone, depending on the reaction conditions



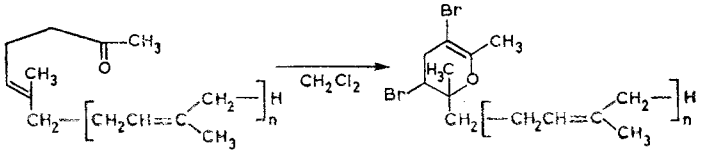
Treatment of substituted allylacetones (LXIX) with $C_6H_5Se^+SbF_4^-$ [61] or phenylselenophthalimide in the presence of iodine [62] also leads to dihydrofuran derivatives (LXX)



Substituted 2-allylcyclohexanones (LXXI) give furan derivatives (LXXII) in this reaction



Dihydropyran derivatives LXXIV are also obtained in quantitative yields in the bromination of γ,δ-unsaturated polyene ketones LXXIII with 2,4,4,6-tetrabromo-2,5-cyclohexadienone [45]

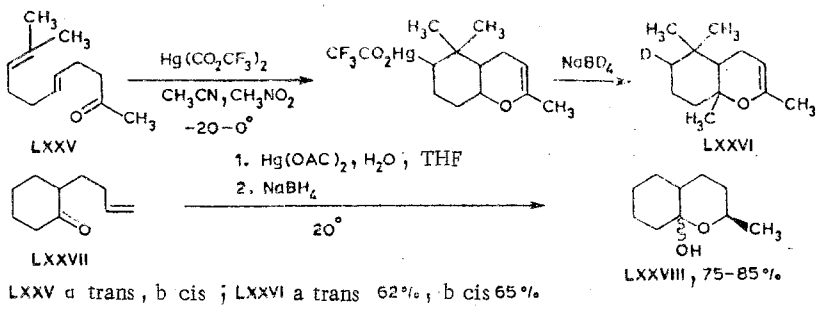


LXXIII

$n = 0-2$

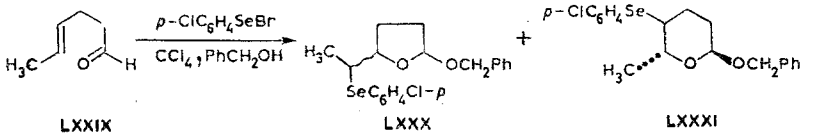
LXXIV

The mercuration of geranylacetone (LXXV) [63] and 2-(3-butenyl)cyclohexanone (LXXVII) [64] leads, respectively, to 2,5,5,9-tetramethylhexahydrochromene (LXXVI) and 2-hydroxy-6-methyl-2,3-tetramethylene-3,4,5,6-tetrahydro-2H-pyran (LXXVIII).



LXXV a trans, b cis; LXXVI a trans 62%, b cis 65%

A mixture of tetrahydrofuran (LXXX) and tetrahydropyran (LXXXI) derivatives is obtained in the reaction of (E)-hexan-4-al (LXXIX) with $4\text{-ClC}_6\text{H}_4\text{SeBr}$ in the presence of benzyl alcohol [65]; LXXX is the kinetically controlled product.



When the reaction is carried out by refluxing for 30 min, it gives primarily the thermodynamically controlled product (LXXXI).

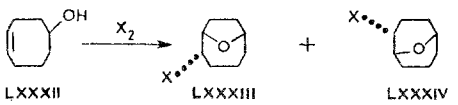
The polycyclic 2-oxaadamantane [66-68], 2,7-dioxaisotwistane [69], and 5,12-dioxapentacyclododecane [70] systems can be obtained in the acetoxymercuration and bromination of cyclic ketones with the corresponding structures.

Thus the following three pathways of electrophilic heterocyclization of unsaturated oxiranes have been established: direct participation of the oxygen atom of the oxiranes in ring formation, cyclization of the glycols that are formed in the hydrolysis of the oxiranes, and cyclization of the products of addition of the electrophile to the double bond of the unsaturated oxiranes.

As a result of heterocyclization, unsaturated aldehydes and ketones are converted to tetra- or dihydrofurans (pyrans), depending on the reaction conditions.

4. Synthesis of Polycyclic Oxygen-Containing Heterocycles

Mixtures of 2-substituted endo-9-oxabicyclo[4.2.1]nonanes (LXXXIII) and endo-9-oxabicyclo[3.3.1]nonanes (LXXXIV) are obtained by the action of mercury salts [71, 72] and iodine [73] on 4-cycloocten-1-ol (LXXXII); LXXXIII are the kinetically controlled products, while LXXXIV are the thermodynamically controlled products.

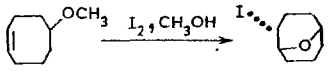


LXXXII LXXXIII LXXXIV

$X_2 = I_2, HgCl_2, Hg(NO_3)_2$

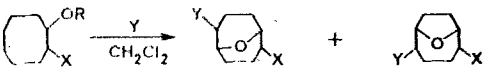
The iodination of cyclooctenol LXXXII in chloroform [73] leads to a mixture of LXXXIII and LXXXIV in a ratio of 1:3. If the iodination of alcohol LXXXII is carried out in methanol [74], only the kinetically controlled product endo-2-iodo-9-oxabicyclo[4.2.1]nonane

(LXXXIII) is obtained. It is interesting that 5-methoxy-1-cyclooctene(LXXXV) under these conditions gives only endo-2-iodo-9-oxabicyclo[3.3.1]nonane (LXXXVI). The rate of iodination of ether LXXXV is considerably lower than the rate of iodination of alcohol LXXXII.



LXXXV LXXXVI

The participation of the methoxy group in electrophilic heterocyclization reactions was demonstrated for the first time in [75] in the case of the chlorination, bromination, and arenesulfenylchlorination of LXXXV and 6-chloro-5-methoxy-1-cyclooctene (LXXXVII). Mixtures of substituted 9-oxabicyclo[3.3.1]nonanes (LXXXVIII) and 9-oxabicyclo[4.2.1]nonanes (LXXXIX) are obtained in quantitative yields in all cases.



LXXXVII LXXXVIII LXXXIX

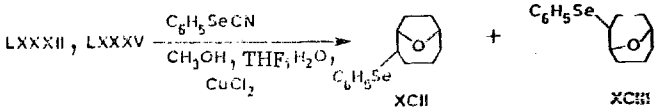
R=H,CH$_3$; X=H,Cl ; Y=Cl$_2$, Br$_2$, ArSCl

The participation of methoxy groups in electrophilic heterocyclization reactions was also observed by these authors in the case of the action of electrophiles on 5-methoxy-1-pentene and 6-methoxy-1-hexene.

A mixture of 2-bromo-9-oxabicyclo[4.2.1]nonane (XC) and 2-bromo-9-oxabicyclo[3.3.1]nonane (XCI) was also obtained in the reaction of cyclooctenol LXXXII with N-bromosuccinimide in water or alcohol [76].

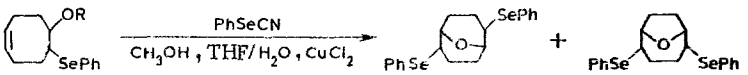
XC, 84% XCI, 16%

A mixture of 2-phenylseleno-9-oxabicyclo[4.2.1]nonane (XCII) and 2-phenylseleno-9-oxabibyclo[3.3.1]nonane (XCIII) is obtained by the action of phenyl selenocyanate in methanol or aqueous THF in the presence of CuCl [77] on alcohol LXXXII or ether LXXXV. The ratio of XCII and XCIII depends on the reaction conditions. Thus a mixture of XCII and XCIII in a ratio of 11:89 was obtained in 80% yield in methanol, whereas a mixture of XCII and XCIII in a ratio of 81:19 was obtained in 99% yield in aqueous THF. It was demonstrated that XCII undergoes isomerization to XCIII. This fact confirms that kinetic and thermodynamic control is observed in the electrophilic heterocyclization reactions of LXXXII and LXXXV.



XCII XCIII

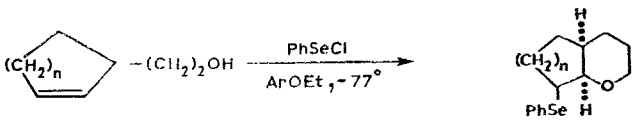
A mixture of isomeric bis(phenylseleno)-9-oxabicyclononanes (XCV and XCVI) is formed in the phenylselenocyanation of 5-hydroxy(methoxy)-6-phenylseleno-1-cyclooctene (XCIV) [77].



XCIV XCV XCVI

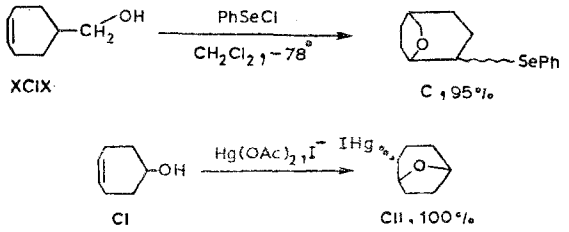
R=H,CH$_3$

Two-ring exo-8-phenylseleno-2-oxabicyclo[3.3.0]octane (XCVIIIa) and exo-5-phenylseleno-7-oxabicyclo[4.3.0]nonane (XCVIIIb) systems were obtained in the reaction of cycloalkenylethanols XCVII with PhSeCl and N-phenylselenophthalsuccinimide [31, 23].



XCVII a n=1 ; b n=2 XCVIII a 84%, b 77%

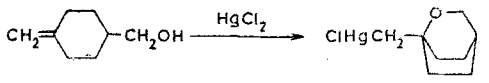
4-Cyclohepten-1-ylmethanol (XCIX) is converted to C under similar conditions [78]. 4-Cyclohepten-1-ol (CI) is converted to 2-iodomercuri-8-oxabicyclo[3.2.1]octane (CII) by acetoxymercuration in the presence of iodide anion [79].



XCIX C, 95%

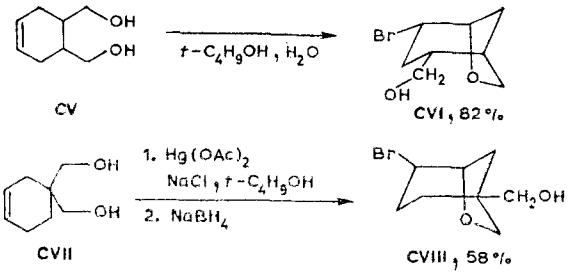
CI CII, 100%

The chloromercuration of 4-methylenecyclohexan-1-ylmethanol (CIII) gives 4-chloromercurimethyl-8-oxabicyclo[2.2.2]octane (CIV) [80]:



CIII CIV, 38%

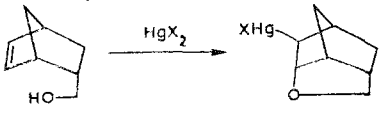
Substituted 6-oxabicyclo[3.2.1]octanes (CVI and CVIII) were obtained by the action of N-bromosuccinimide on cis-1,2-bis(hydroxymethyl)-4-cyclohexene (CV) [81] and of $Hg(OAc)_2$ on 4,4-bis(hydroxymethyl)-1-cyclohexene (CVII] [82]. Of the two possible bicyclic [2.2.2] and [3.2.1] skeletons, only the latter is obtained.



CV CVI, 82%

CVII CVIII, 58%

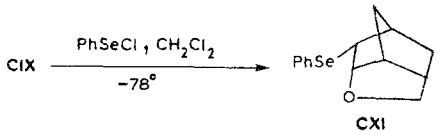
It has been shown [83] that the mercuration of endo-5-hydroxymethyl-2-norbornene (CIX) gives tricyclic ether (CX).



CIX X = Cl, OAc CX

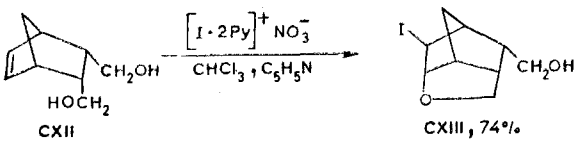
The rate of acetoxymercuration of CIX is higher by a factor of 100 than the rate of acetoxymercuration of the exo epimer [54]; this confirms participation of the adjacent hydroxy group in intramolecular heterocyclization in the case of the endo epimer. The participation of the OH group in the reaction is realized via a trans scheme [84].

If the complex of piperidine with $HgCl_2$ is used as the electrophile, CX is obtained in 60% yield [85], whereas in the case of benzeneselenyl chloride cyclic product CXI is formed in 93% yield [86].

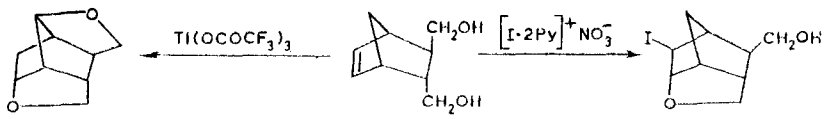


CXI

The reaction of the $[I \cdot 2Py]^+NO_3^-$ complex with endo-cis-5-norbornenylbis-2,3-methanol (CXII) in chloroform—pyridine [26] leads to the formation of tricyclic product CXIII, whereas trans-5-norbornenylbis-2,3-methanol (CXIV) under the same conditions is converted to isomeric CXV. It is interesting that diether CXVI was obtained by the action of $Tl(OCOCF_3)_3$ on CXIV [87].

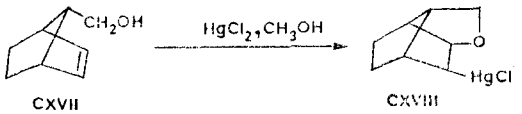


CXII CXIII, 74%



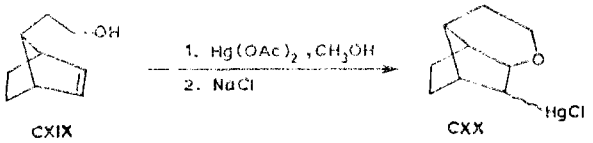
CXVI, 36% CXIV CXV, 86%

endo-7-Hydroxymethyl-2-norbornene (CXVII) is converted to cyclic ether CXVIII upon chloromercuration [88]. As in the case of carbinol CIX, attack of the electrophile takes place via a trans-addition scheme.



CXVII CXVIII

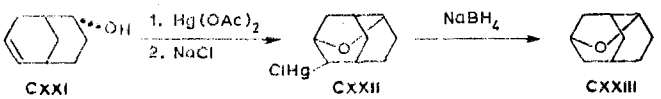
Under similar conditions endo-7-(2-hydroxyethyl)-2-norbornene (CXIX) is converted to a mixture of cyclic products with unestablished configurations (CXX) [89].



CXIX CXX

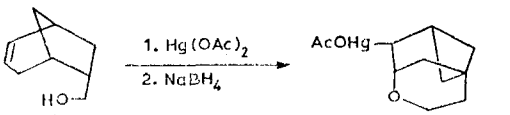
exo-7-(2-Hydroxyethyl)-2-norbornene gives only products of addition to the double bond.

As a result of acetoxymercuration, endo-bicyclo[3.3.1]non-2-en-6-ol (CXXI) is converted to 10-chloromercurioxaisotwistane (CXXII) [90], the demercuration of which leads to 2-oxaisotwistane (CXXIII):



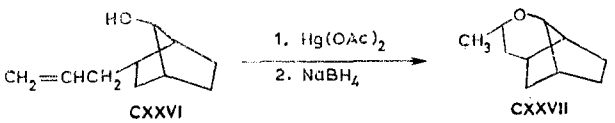
CXXI CXXII CXXIII

5-Oxaprotoadamantane (CXXV) was obtained by similar treatment of endo-6-(hydroxymethyl)-bicyclo[3.2.1]-2-octene (CXXIV) [91].



CXXIV CXXV, 83%

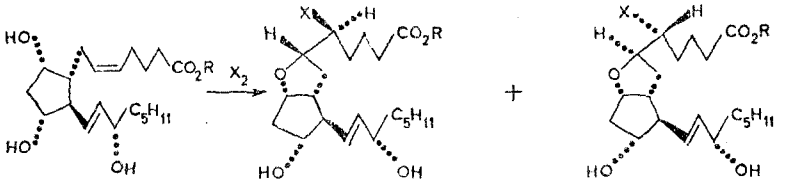
A similar transformation of 1-allyl-7-norbornanol (CXXVI) leads to tricyclic ether CXXVII [92].



CXXVI CXXVII

The 3-oxa- and 12-oxatetracyclododecane [93-96], 2,7-dioxaisotwistane [69, 97, 98], and 5,12-dioxapentacyclododecane [70] systems were obtained by acetoxymercuration of the alcohols with the corresponding structures.

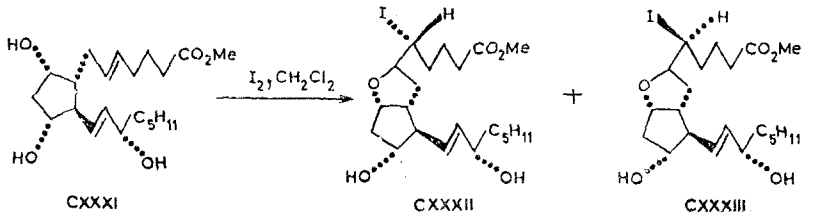
The electrophilic heterocyclization of unsaturated alcohols is used for the preparation of several physiologically active substances. The reaction of prostaglandin methyl ester CXXVIIIa with iodine in water [99] gave CXXIXa or CXXXa:



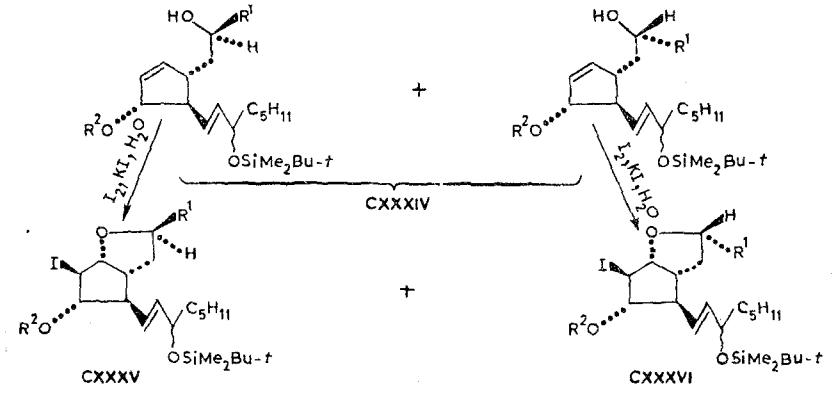
CXXVIII–CXXX a R=CH_3, X=I; b R=CH_3, X=SePh; c R=CH_3, X=Br; d R=CH_3, X=H; e R=X=H

The iodination and treatment of ester CXXVIII with N-bromosuccinimide [100] in CH_2Cl_2 leads, respectively, to mixtures of bicyclic CXXIXa and CXXXa or CXXIXc and CXXXc systems with preponderance of compounds of the CXXX type. A similar mixture was also obtained in the reaction of ester CXXVIII with PhSeCl [101]. Its acetoxymercuration [100] with subsequent reduction of the mercury-containing products with $Na(CN)BH_3$ gives a mixture of CXXIXd and CXXXd in a ratio of 1:2. The same mixture of diastereomers CXXIXe and CXXXe was obtained by acetoxymercuration of ester CXXVIIIe and subsequent reduction of the mercuration products with $NaBH_4$ [102].

The iodination of 5-trans-prostaglandin CXXXI in CH_2Cl_2 leads to CXXXII and CXXXIII in a ratio of 1:6 [100].



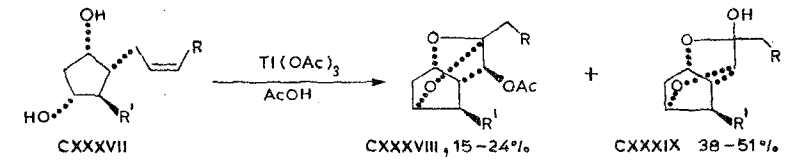
Upon iodination in water the mixture of diastereomeric alcohols CXXXIVa [102] gives iodo derivatives CXXXVa and CXXXVIa in a ratio of 5:1.



CXXXIV–CXXXVI a $R^1=(CH_2)_4CH_2OH$, $R^2=H$; b $R^1=(CH_2)_4COOH$, $R^2=H$; c $R^1=(CH_2)_4COOH$, $R^2=SiMe_2Bu\text{-}t$

Primarily CXXXVb was obtained in the iodination of acid CXXXIVb [103], whereas the iodocyclization of prostaglandin CXXXIVc leads to a mixture of diastereomers CXXXVc and CXXXVIc in a ratio of 6:1 [102].

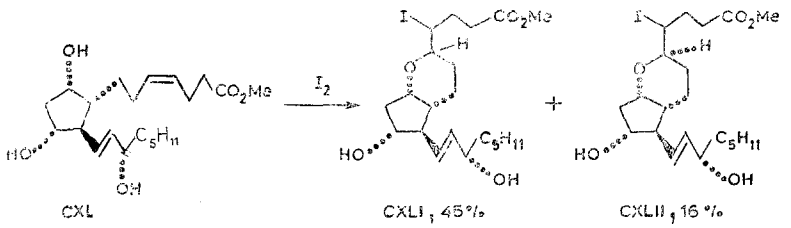
The conversion of prostaglandins of the F type (CXXXVII) to tricyclic prostacyclines CXXXVIII and CXXXIX by means of thallium triacetate [104] is interesting:



CXXXVII–CXXXIX a $R=(CH_2)_3COOCH_3$, $R'=CH{=}CHCH(OH)(CH_2)_4CH_3$;

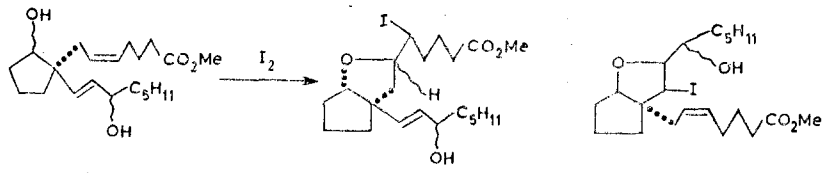
b $R=(CH_2)_3COOCH_3$, CH_3, $R'=CH_2OC_6H_5$

The iodination of prostaglandin methyl ester CXL leads to a mixture of diastereomeric prostacyclines CXLI and CXLII [105].



CXL CXLI, 45% CXLII, 16%

Under similar conditions prostaglandins CXLIII are converted to, respectively, a mixture of diastereomers CXLIV and individual isomer CXLV [106].



CXLIII CXLIV, 58% CXLV, 67%

The electrophilic heterocyclization of unsaturated alcohols is also used in the preparation of several antibiotics [107, 108] and antidepressants [109].

Thus, electrophilic heterocyclization is of interest not only from a theoretical point of view but also serves as a convenient method for the stereospecific synthesis of medicinal preparations.

5. Kinetics of the Electrophilic Heterocyclization Reactions of Unsaturated Alcohols

It has been established that the rates of iodocyclization of unsaturated alcohols, phenols, ketones, and oxiranes are described by a second-order kinetic equation (first-order in each of the reagents). A study of the kinetics of the chloromercuration [110, 111] and iodination [21, 29] of substituted 2-allylphenols and unsaturated alcohols showed that both the free phenols and phenoxide ions can undergo the reactions in the case of phenols; the phenoxide ions are more active by three orders of magnitude than the free phenols. The rate constants for the iodocyclization of 4-substituted 2-allylphenols [1] increase as their pK_α values increases.

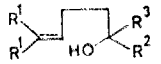
The rate constant for the chloromercuration of pent-4-en-1-ol is greater by a factor of 450 than in the case of its methyl ether [1], which confirms participation of the adjacent hydroxy group of pent-4-en-1-ol in electrophilic heterocyclization.

In a study of the effect of the length of the chain of $CH_2=CH(CH_2)_nOH$ on their rates of iodination [24] it was found that the maximum rate is observed for the alcohol with n = 3, which is in agreement with the formation of a tetrahydrofuran ring.

It follows from Table 2 that the introduction of α substituents relative to the hydroxy group of pent-4-en-1-ol leads to an increase in their iodocyclization rates [37]. Thus the rate of iodination increases by a factor of ∿22 on passing from pent-4-en-1-ol to 1-phenylpent-4-en-1-ol (XXXIIc). The increase in the rate of iodination in series of compounds of the XXXII type can hardly be explained only by the electronic effect of the α substituents on the hydroxy group, since in these cases it must be assumed that the difference in the pK_α values of the alcohols will be slight. The increase in the rate of iodocyclization in this series is associated with the conformational effect of the α substituents, the introduction of which shifts the conformational equilibrium to favor the more reactive gauche conformations.

It is also apparent from Table 2 that in the series of alcohols XXII the rate of iodocyclization increases appreciably as compared with the XXXII series [39]. For example, the rate constant for the iodination of 1,5-di-methylhex-4-en-1-ol (XXIIa) is higher by a factor of 30 than in the case of 1-methylpent-4-en-1-ol (XXXIIa). This increase in the reactivity is associated with an increase in the "nucleophilicity" of the double bond in alcohol XXIIa due to the inductive and hyperconjugation effects of the methyl groups attached to the douhle bond [112].

TABLE 2. Kinetic and Thermodynamic Parameters of the Iodocyclization of Unsaturated Alcohols (XXII and XXXII)



Compound	R^1	R^2	R^3	k, liters/mole·sec (20°C)	$\Delta E^{\neq}$, kcal/mole	$-\Delta S^{\neq}$, eu	lg A
XXXII	H	CH_3	H	4,9±0,3	11,0±1,0	19,9±3,6	8,8
XXXII	H	CH_3	C_2H_5	13,5±1,0	10,5±1,3	19,6±3,6	8,9
XXXII	H	H	C_6H_5	34,1±1,5	9,2±0,9	22,1±3,4	8,4
XXII	CH_3	CH_3	H	127,4±4,3	9,7±0,8	17,7±2,7	9,3
XXII	CH_3	H	C_6H_5	24,5±1,6	9,1±1,0	23,1±3,4	8,2
XXII	CH_3	CH_3	C_2H_5	23,8±1,4	9,7±1,0	21,1±3,3	8,6

The rate of iodocyclization of 5-hydroxymethyl-2-norbornene (CIX) [113] is higher by approximately two orders of magnitude than in the case of pent-4-en-1-ol. This difference in the rates of iodination is explained by the fact that, in contrast to pent-4-en-1-ol, for which the reaction proceeds through a slightly polarized π complex of iodine with the double bond [21, 29], in the case of the iodocyclization of alcohol CIX the formation of a polarized σ complex of iodine with the conjugated double bond of 5-hydroxymethyl-2-norbornene is postulated [113].

A study of the kinetics of the iodination of cis- and trans-2-allylcyclohexanols Ia,b has shown that the rate constants for their iodocyclization are close and are approximately an order of magnitude higher than the rate constants for the iodination of pent-4-en-1-ol; this is explained by the higher degree of orderliness of the transition state for the cyclization of 2-allylcyclohexanols.

A similar pattern is also observed in the iodination of allylacetone and 2-allylcyclohexanone [60], in which the increased reactivity of the latter is primarily associated with the favorable structure of this molecule, which promotes the formation of a cyclic transition state.

Thus the rate constants for the iodocyclization of unsaturated alcohols, phenols, ketones, and oxiranes depend on the nature, structure, configuration, and conformation of the unsaturated molecule, as well as on the "nucleophilicity" of its double bond.

At the time that the present review was being edited new communications regarding the heterocyclization of unsaturated alcohols and phenols [114-125], oxiranes [126, 127], and ketones and aldehydes [128, 129] had already been published.

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REACTIONS OF ALDEHYDES OF THE FURAN SERIES.

2.* OXIDATION WITH SODIUM HYPOHALITES

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UDC 66.094.3:547.724:543.87

The conditions for the oxidation of formylfurans with sodium hypobromite and hypochlorite that promote an increase in the yields for the furancarboxylic acids were investigated. The usual composition of the hypohalite mixture [NaOH]:[X_2] = 3 gives low yields of the furancarboxylic acids, particularly on the basis of 5-methylfurfural. Doubling the relative percentage of alkali promotes an increase in the efficiency of the reaction. An interpretation of the process is given.

The corresponding furancarboxylic acids are formed in up to 90% yields in the oxidation of furfural [2, 3] and its halo derivatives [4], as well as 2,5-diforylfuran [5], with sodium hyperbromite or hypochlorite (NaOX). The oxidation of 5-methylfurfural (I) with hypohalites has not been described. Our attempt to oxidize this compound with sodium hypobromite under the conditions of the method in [3] showed that 5-methylpyromucic acid (II) is formed in no higher than 20% yield. The bulk of aldehyde I remains unchanged. An unidentified oil that decomposed with HBr evolution was extracted as a side product from the reaction mixture. Regulation of the temperature of the mixture over the range −10 to +5°C did not make a significant difference in the yield of acid II.

The known methods for the preparation of acid II are based on the oxidation of aldehyde I with molecular oxygen with catalysis by silver oxide [6-8] and potassium ferrate [9], its disproportionation via the Cannizzaro reaction [10], and on the chloromethylation of pyromucic acid ester (III) with subsequent reduction of the chloromethyl group to a methyl group and saponification of the ester [11]. These methods have little applicability because of the low yields of the acid or the preparative complexity. The development of an efficient method for the preparation of acid II, which can be used as the basis for the preparation of the industrially important compound furan-2,5-dicarboxylic acid, as well as for use in the syntheses of biologically active substances, makes it possible to make it more accessible. The starting compound, viz., 5-methylfurfural, is accessible, inasmuch as it is a side product of the hydrolysis industry.

In the present paper we present the results of a study of the conditions for the oxidation of 5-methylfurfural (I) with hypobromite and hypochlorite that facilitate the production of methylpyromucic acid in high yield, and we also give an interpretation of the oxidation of

*See [1] for Communication 1.

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