ELECTROPHILIC HETEROCYCLIZATION OF UNSATURATED CARBOXYLIC ACIDS IN THE SYNTHESIS OF LACTONES (REVIEW)

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Data on the electrophilic-heterocyclization reactions of γ,δ- and δ,ε -unsaturated carboxylic acids are correlated. The use of this reaction for the synthesis of substituted mono-, bi-, tri-, and polycyclic γ- and δ-lactones is demonstrated. Data on the regioselectivity of the addition of electrophiles and the stereochemistry of the resulting cyclization products are presented.

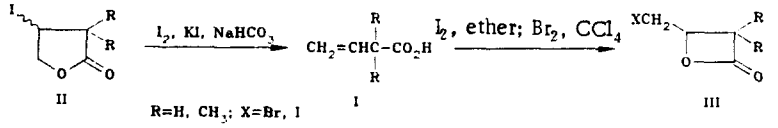
The electrophilic intramolecular heterocyclization of unsaturated polyfunctional compounds is widely used for the synthesis of heterocycles [1-8]. The use of this reaction for obtaining lactones was demonstrated for the first time in the case of the bromination of diallylacetic and diallylmalonic acids [4]. The recent increased interest in this reaction is due to the fact that it proceeds, in most cases, regio- and stereoselectively. The resulting substituted lactones are often intermediates in the synthesis of more complex molecules.

Review papers [5, 6] have been devoted to the electrophilic intramolecular heterocyclization of unsaturated carboxylic acids to lactones. Individual problems in the electrophilic lactonization of carboxylic acids have been examined in monographs [7, 8]. Problems involving the reactivities of unsaturated acids and the regio- and stereoselectivity of electrophilic lactonization were discussed in part in these publications.

In the present paper we examine data published primarily in the last 10-15 yr and discuss the effect of the structure, configuration, and conformation of the unsaturated acids, the nature of the electrophile, and the solvolytic properties of the medium on the stereochemical peculiarities of lactonization.

1. Electrophilic Heterocyclization of Unsaturated Carboxylic Acids of the Aliphatic and Aliphatic-Aromatic Series

The formation of β-lactones in the bromination of dimethylmalonic and dimethylfumaric acids, as well as salts of cis- and trans-stilbenecarboxylic acids, is known [5]. δ-Lactones III are obtained in the bromination [9] and iodination [10, 11] of but-3-noic acids I; γ-lactone II was isolated in the iodination of I with iodine in water (I_2, KI, $NaHCO_3$, H_2O), while β-lactone III was isolated in the reaction with iodine in ether.



The halogenation of 2- and 4-methylpent-3-enoic acids leads to the formation of γ-lactones [12, 13]. The reaction proceeds trans-stereoselectively.

Vinylacetic acid and β- and γ-alkyl-substituted vinylacetic acids react with PhSeCl to give γ-lactones [14].

Palladium complexes can also be used as electrophilic agents for the synthesis of γ- and δ-lactones from saturated carboxylic acids [15].

Chlorolactone V was obtained in the chlorination of acid IV with Chloramine-T [16], whereas 5-hexenoic acid gives the corresponding δ-chlorolactone upon chlorination under these conditions. Lactones VI and VII were obtained by the action of aryltellurium trichlorides [17] and perfluoroalkylphenyliodonium trifluoromethanesulfonate [18] on acid IV. The corresponding γ-lactone was obtained by treatment of acid IV with N-phenylselenophthalimide (N-PSP) and N-phenylselenosuccinimide (N-PSS) [19], as well as PhSeCl, $PhSeNEt_2$, $PhSeCl_3$, and substituted benzeneselenyl bromides [20].

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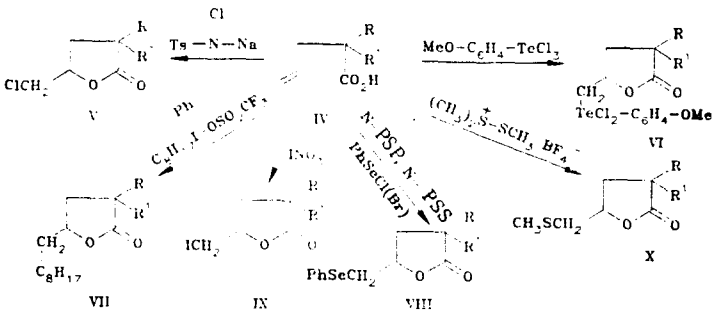
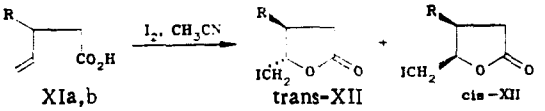


V, VII, IX, X R=R¹=H; VI **a** R=R¹=H, **b** R=H, R¹=CH₃, **c** R=R¹=CH₃, **d** R=R¹=C₆H₅; VIII R=R¹=C₆H₅

γ-Lactones are formed in the reaction of PhSeCl with 3- and 4-methyl-4-pentenoic and 4-methyl-3-pentenoic acids [20]. γ-Lactones IX and X were obtained by treatment of acid IV with, respectively, iodine nitrate [21] and dimethyl(methylthio)sulfonium tetrafluoroborate [22]. It follows from the data presented that the nature of the electrophile and the nature of the substituents in the α and β positions relative to the carboxy group have virtually no effect on the size of the resulting lactone in the cyclization of pentenoic acids IV.

The iodolactonization of acids XI and their esters with iodine in CH_3CN leads to the formation of primarily trans-isomer XII [23, 24]. N-Iodo-succinimide (NIS) in $CHCl_3$ [25] reacts with acid XI with the formation of primarily cis-lactones XIIa, b.



XIIa R=CH₃, trans: cis - 10:1 (84%), b R=C₆H₅, trans: cis 20:1 (98%)

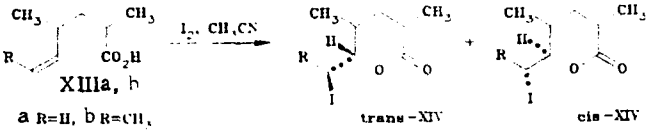
The ratios of the cis and trans isomers are 3:1 (for XIa) and 4:1 (for XIb). The authors explain the formation of primarily the cis isomers in the following way: in the case of iodolactonization with the participation of NIS the reaction proceeds with the formation of an intermediate iodonium cation, the attack on which by the carboxy group may lead to cis products. In the iodination with iodine in CH_3CN it is assumed that lactonization proceeds as synchronous trans addition of iodine and the carboxy group.

A decrease in the stereoselectivity of the reaction is observed in the lactonization of acid XIb by means of $Hg(OAc)_2$ and N-PSP [26]. The ratios of the trans- and cis-lactones in these cases are 6:1 and 1:1, respectively.

Appreciable stereocontrol is achieved in the iodolactonization of 3- and 4-methyl-5-hexenoic acids, as well as 2,4-dimethyl-5-hexenoic acid [8, 27]. In the first case δ-lactones are formed when the reaction is carried out under thermodynamically controlled conditions (the ratio of the cis and trans isomers is 1:10), whereas in the second case cis-1,3-products are formed (the cis:trans ratio is 6:1), and in the third case trans-1,2-products are formed (the cis:trans ratio is 1:20). 2-Methyl-5-hexenoic acid, which gives a mixture of cis- and trans-1,4-disubstituted δ-lactones in a ratio of 1:1.1, constitutes an exception. Snider and Johnston [28] were able to obtain all four regio- and stereoisomers in the halocyclization of 3,5-dimethyl-4-pentenoic acid. The regioselectivity of the reaction is rather low. The ratio of the isomeric δ-lactones is 1:7. The iodolactonization of 3,3-bis(carboxymethyl)-5-butyl-4-pentenoic acid is completely regioselective and leads only to the γ-lactone [29].

The sulfenylchlorination of 5Z- and 5E-eicosenoic acids gives, respectively, the threo- and erythro-δ-lactones with a high degree of stereoselectivity [30].

High stereoselectivity of the lactonization reaction is observed in the iodination, mercuration, and phenylselenation of 2,4-dimethyl-5-hexenoic acids [23, 26]. For example, the iodolactonization of XIIIa leads to the formation of δ-lactones XIV with a trans:cis ratio of 20:1 (89%), while XIIIb gives δ-lactones XIV with a trans:cis ratio of 10:1 (52%).

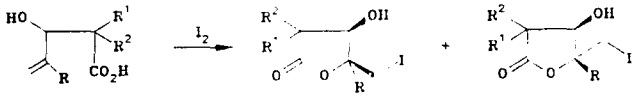


a R=H, **b** R=CH₃

Different results were obtained in the iodolactonization of 3-hydroxy-4-pentenoic acids XV. Under kinetically controlled conditions of iodination of these acids (I_2, aqueous $NaHCO_3$, THF—ether) [10] primarily the thermodynamically less stable cis-lactones XVI were obtained [31, 32]. The trans isomers XVI are formed in 4-7% yields. The presence of methyl groups attached to the $C_{(2)}$ atom decreases the stereoselectivity of the reaction and in some cases leads to the formation of primarily the trans isomer. Replacement of the OH group attached to the $C_{(3)}$ atom by a CH_3 group promotes the formation of a mixture of cis and trans isomers (60:40).

Stereoselectivity of the lactonization is also retained in the iodination of unsaturated acids that contain an OH group attached to the $C_{(2)}$ atom [33]. The formation of primarily cis-lactones is observed in this case. The stereoselectivity of the iodolactonization reaction is explained in the following way [30, 31]: the conformer in which the OH group attached to the $C_{(3)}$ atom and the substituent attached to the $C_{(4)}$ atom are maximally remote from one another primarily participates in the formation of the transition state.

An equilibrium mixture of all four possible regio- and stereoisomeric lactones is formed initially in the iodination of 2-hydroxy-3,5-dimethylhexene-4-carboxylic acid in water; upon standing this mixture is converted to a mixture of 3,4-trans- and 3,4-cis-γ-lactones in a ratio of 3:1 [8].



XV cis-XVI trans-XVI

R, R^1, R^2=H, CH_3

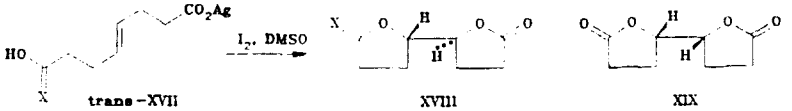
The diastereoselective formation of γ-lactones is observed in the iodination [34] and bromination with N-boromosuccinimide (NBS) [35] and with bromine [36] of substituted 2-amino-3-hydroxy(methyl)-4-pentenoic acids. The iodolactonization of 2-fluoro-3-methyl-4-pentenoic acids under conditions of thermodynamic control leads primarily to the γ-lactone in which the fluorine atom and iodomethyl group are cis oriented [37]. A similar result was obtained in the iodination of a substituted 3-trifluoromethyl-4-pentenoic acid [38]. The iodocyclization of 5,5-difluoro-4-pentenoic acids proceeds regioselectively with the formation of the corresponding δ-lactones [39].

As a result of iodolactonization, 2-alkyl-2-thiomethoxy-4-pentenoic acids give unsaturated lactones [40].

A study of the rates of iodolactonization of 2-alkyl-substituted 4-pentenoic acids [41] and the iodocyclization [42] and mercuricyclization [43, 44] of phenyl esters of 4-pentenoic acids showed that the rate of cyclization depends on the state of the conformational equilibrium of the unsaturated molecules and increases with an increase in the volume of the substituents. A similar pattern is observed in the iodination of 3-methyl- and 2,2- and 3,3-disubstituted 4-pentenoic acids [45-47].

Spirobislactones were obtained in the reaction of diethyl diallylmalonate with iodine [25], PhSeCl [48, 49], and Chloramine-T [16].

Bislactones XVIII are formed in the iodination of silver salts of unsaturated trans-di- and -monocarboxylic acids XVII in DMSO in the presence of silver acetate [50, 51]. cis-Dihydromuconic acid gives bislactone XIX.



trans-XVII XVIII XIX

X=O, H_2

A mixture of regioisomeric macrocyclic lactones is formed in the reaction of N-PSP with tridecene-12-carboxylic acid in the presence of camphorsulfonic acid [52]. The corresponding 16-membered macrolactone was similarly obtained in 54% yield.

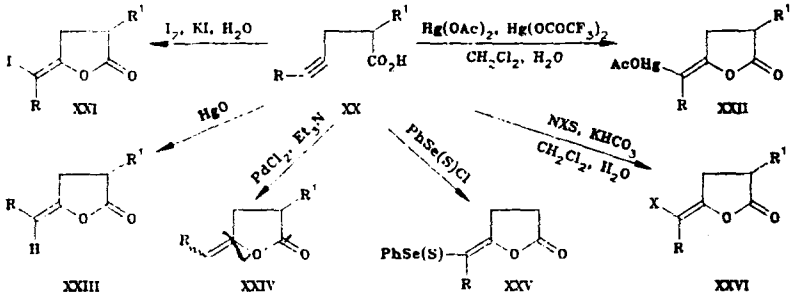
Lactones are also formed in the halogenation of amides of unsaturated carboxylic acids [53, 54]. This reaction often proceeds more stereoselectively than the lactonization of the corresponding unsaturated acids. The halolactonization of amides of 2-R-substituted

pentene(4-hexene)carboxylic acids with halosuccinimides proceeds 1,3-trans-stereoselectively. The stereoselectivity of the reaction depends on the nature of the halogen in NXS [55]. The lowest stereoselectivity is observed in the case of the halogenation with N-chlorosuccinimide. This is probably due to the participation of ion pairs of various natures in the reaction. In the case of iodo- and bromosuccinimides participation of solvate-separated ion pairs in the reaction is preferred, while intimate ion pairs are formed along with solvate-separated ion pairs in the case of chlorosuccinimide. In the iodolactonization of 3-methylpentene-4-carboxylic acid dimethylamide with iodine in aqueous DMF the stereoselectivity decreases sharply but remains high in the iodolactonization of 2,3-disubstituted pentene-4-carboxylic acid dimethylamides; this is evidently explained by the participation of one of the preferred conformations of the acid in the reaction.

Lactones XXI-XXIII were obtained in the iodination [5] and mercuration [56-58] of pentyne-4-carboxylic acids XX. The Z-isomeric lactones are primarily formed as a result of mercuricyclization. Halolactonization by means of NXS (X = Cl, Br, I) proceeds stereoselectively and leads primarily to E-isomeric lactones XXVI [57]. The lactonization of acid XX with thio- and selenosulfenyl chlorides gives lactones XXV [59]. Isomeric lactones XXIV were obtained by the action of palladium salts [60, 61] on acid XX. Primarily the trans products (84-100%) are formed.

In the presence of $PdCl_2$ 3-butynoic acid lead to γ-lactones, whereas 5-hexynoic acid gives the corresponding δ-lactone under these conditions [60].

The halolactonization of 2-acetamido- or 2-benzamido-2-R^1-4-pentynoic acids (R^1 = H, $CH_2C_6H_5$) by means of NBS and NIS [62] leads to γ-lactones in good yields.



XXI, XXV R=R¹=H, XXII R=Cl, Br, CH_3, $(CH_3)_3Si$, R¹=H, C_6H_5; XXIII R=H, C_6H_5, R¹=H, $(-CH_2O)_2-C(CH_3)-$; XXIV R=H, CH_3, C_6H_{13}, C_6H_5 R¹=H, C_4H_9, C_6H_{13}, C_6H_5, $CH_2C_6H_5$; XXVI R=H, CH_3, R¹=H, X=Cl, Br, I

The mercuricyclization of acetamido(benzamido)-5-hexynoic acids gives only 3,4-trans-tetrahydro-2-pyranones, while their iodolactonization leads to mixtures of diastereomeric cis-(3R,4S)- and trans-(3R,4R)-3-acylamino-4-phenyl-6(E)-iodomethylidenetetrahydro-2-pyranones with preponderance of the latter [63]. The bromination of methyl and isopropyl 2-(phenylethynyl)benzoates gives 4-bromo-3-phenylisocoumarin [64]. The reaction proceeds regioselectively with the formation of only the δ-lactone.

The thermal cyclization of dipropargylmalonic acid in the presence of HgO leads to the formation of a spirobislactone [65].

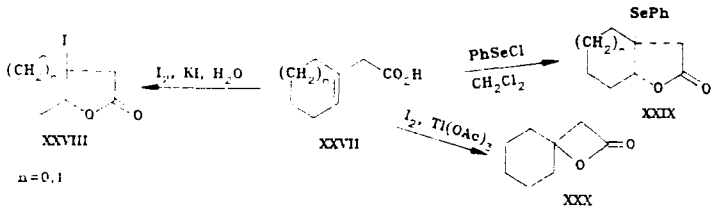
Examples of the formation of unsaturated lactones as a result of the electrophilic lactonization of allenecarboxylic acids and their esters [66], dienecarboxylic acids [67-69] and esters of unsaturated acids that contain simultaneously double and triple bonds [67] are known.

2. Lactonization of Carbocyclic Unsaturated Carboxylic Acids

Numerous examples of the electrophilic lactonization of unsaturated mono- and bicyclic carboxylic acids have been presented in a review [5] and in other publications [20, 70-72]. It follows from these publications that γ-lactones with cis fusion of the lactone ring and the remainder of the molecule are formed most readily. These principles are observed in many examples of the electrophilic lactonization of unsaturated carbocyclic carboxylic acids.

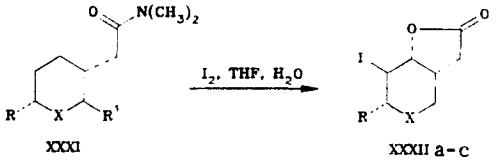
Thus iodolactone XXVIII and γ-lactone XXIX were obtained in almost quantitative yields in the iodination [73] and phenylselenochlorination [20, 72] of 1-cycloalkenylacetic acids

XXVII. The iodination of acid XXVII (n = 1) in the presence of thallium acetate in CH_2Cl_2 gives a mixture of β-lactone XXX and iodolactone XXVIII (1.5:1) [13].



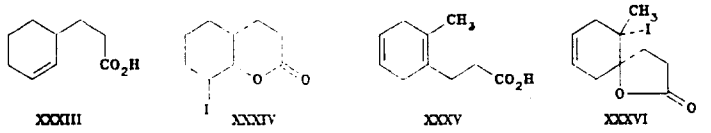
The iodolactonization [13, 73, 74] and phenylseleno(sulfeno)lactonization of 2-cycloalkenylacetic acids by means of PhSeCl [71, 72, 75, 76] and PhSCl [76] or N-PSP and N-PSS [19] lead to the corresponding substituted γ-lactones. The reaction of these acids with aryltellurium trichlorides [17] also gives γ-lactones. The corresponding bi- and tricyclic γ-lactones were obtained in the iodination of 3-cyclopentenyl-1,2-diacetic acid [77] and 2-cycloalkenylpropenoic acids [78-81]. The iodination [70, 82, 83] and phenylselenochlorination [72, 84] of 2,2-disubstituted 2-cyclohexenylacetic acids lead to γ-lactones. The stereochemistry of the iodolactones was proved rigorously by PMR spectroscopy [85-87].

Bicyclic systems XXXIIa-c are readily obtained in the iodination of 2-cyclohexenylacetic acid dimethylamides XXXI [88-90]. This reaction is used for the stereocontrolled synthesis of thromboxane B_2 from D-glucose [91]. The lactones obtained by the iodolactonization of the corresponding 2-cyclohexenylacetic acids are intermediates in the synthesis of thromboxanes and vitamin D_2 [92-94].



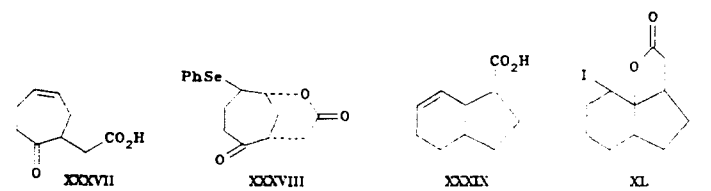
a R=R¹=H, X=CH₂, b R=R¹=H, X=O, c R=OCH₃, R¹=CH₂OH, X=O

The iodination of 2-cyclohexenylpropionic acid (XXXIII) gives cis-fused bicyclic δ-lactone XXXIV [95], while 1,4-cyclohexadienylpropionic acid XXXV gives spirolactone XXXVI [96].

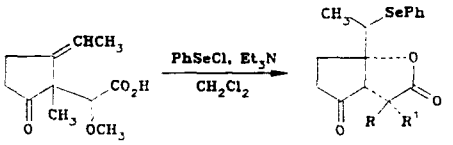


Upon reaction with iodine in CH_3CN, phenylselenium chloride in CH_2Cl_2 and mercuric acetate in CH_3OH, 1,3-cyclohexadienylacetic acid is converted to the corresponding substituted γ-lactones [97, 98]. 1,3-Cycloheptadienylacetic acid reacts with PhSeBr in CH_2Cl_2 in the presence of triethylamine to give a mixture of three γ-lactones [98], whereas 3-cycloheptenylacetic acid (XXXVII) under similar conditions undergoes cyclization to bicyclic δ-lactone XXXVIII [99].

The formation of hydrindan system XL in the iodolactonization of unsaturated acid XXXIX proceeds stereoselectively [100].



Under the influence of phenylselenium chloride the exocyclic double bond of epimeric acids XLI gives a mixture of γ-lactones XLIIa, b in a ratio of 43:57 [101]. The exocyclic double bond of the cyclohexane system reacts similarly [102].



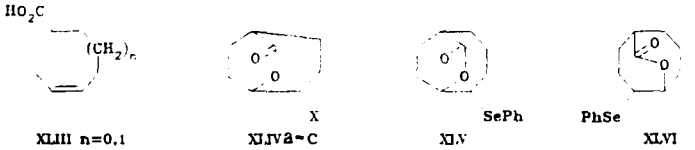
XLI XLII a,b

XLII a R=OCH_3, R^1=H, b R=H, R^1=OCH_3

Upon reaction with PhSeCl, cis- and trans-stilbene-2-carboxylic acids are converted to mixtures of epimeric δ- and γ-lactones [20].

The reaction of 3-cyclohexenecarboxylic acid with iodine [103, 104], benzeneselenyl chloride [72, 105], and methane(benzene)sulfenyl chlorides [22, 76] leads to the corresponding γ-lactones, whereas its reaction with Chloramine-T gives a mixture of γ- and δ-lactones in a ratio of 24:41 [16]. Various substituted 3-cyclohexenecarboxylic acids readily undergo electrophilic lactonization [106-108].

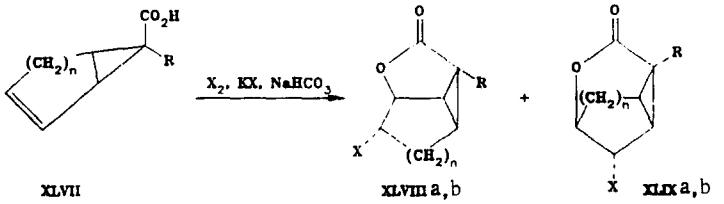
4-Cycloheptenecarboxylic acid (XLIII, n = 0) reacts with PhSeSl and PhSCl [76], as well as $(CH_3)_2S^+-S-CH_3$ [22], to give lactones XLIVa-c. The phenylselenochlorination of 4-cyclooctenecarboxylic acid (XLIII, n = 1) leads to a mixture of lactones XLV and XLVI in a ratio of 4:1 [20].



XLIII n=0,1 XLIVa-c XLV XLVI

XLIVa X=SePh, bX=SPh, c X=SCH_3

A mixture of tricyclic γ-XLVIIIa and δ-XLIXa lactones in a ratio of 5:1 was obtained in the bromination of unsaturated acid XLVIIa [109].

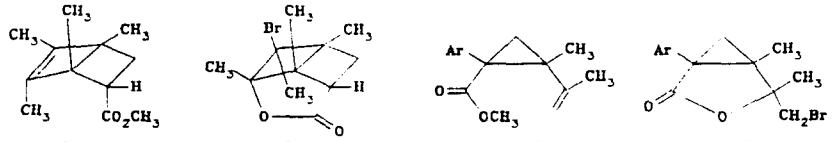


XLVII XLVIII a,b XLIX a,b

XLVIII, XLIX aR=H, X=Br,I, n=1; b R=$(CH_2)_2CH=C(CH_3)_2$, X=I, n=2

The iodination of these acids leads only to δ-iodolactones XLIXa, b in 76% and 88% yields, respectively [110, 111].

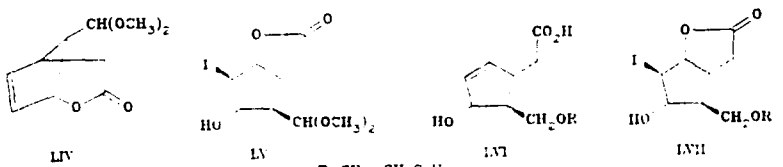
The bromination of bicyclohexenecarboxylic acid ester L, as well as 2-vinylcyclopropanoic acid ester LII, leads to the formation of exo-bromolactone LI and bicyclic γ-lactone LIII [112, 113].



L LI LII LIII

Ar = $-C_6H_4-NO_2$

Examples of the formation of bi-, tri-, and polycyclic lactones, which are intermediates in the synthesis of various natural compounds, are known [114-117]. The effect of alkyl groups on the regioselectivity of the formation of δ- and γ-lactones was demonstrated in the case of the bromination of alkyl-substituted 1,4-dihydrobenzoic acids [118, 119].



LIV LV LVI LVII

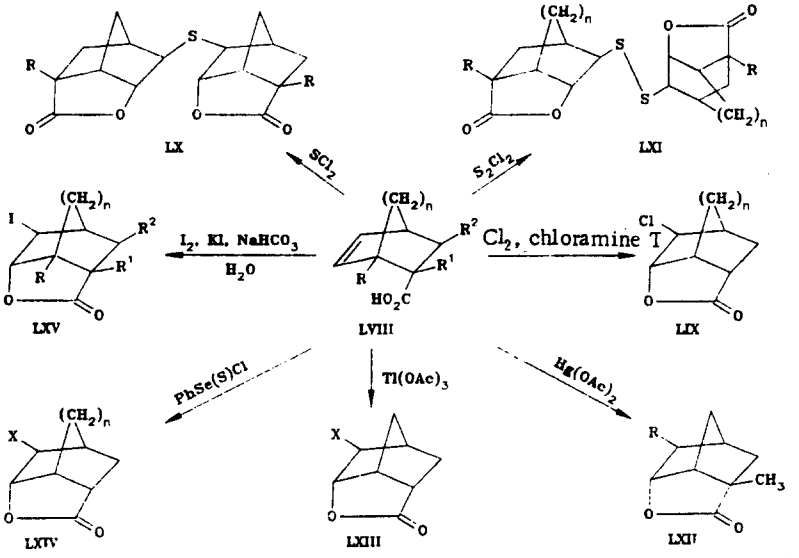
R=CH_3, $CH_2C_6H_5$

The iodination of lactone LIV leads to the Corey iodolactone LV — the universal precursor of prostaglandins [120, 121] — while unsaturated acids LVI give iodolactones LVII [122-128]. The electrophilic lactonization of unsaturated carboxylic acids is widely used for the synthesis of prostacyclins [76, 129, 130].

3. Lactonization of Polycyclic, Carcass, Unsaturated Carboxylic Acids

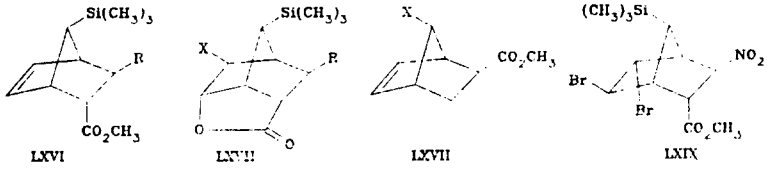
Unsaturated acids that have a rigid molecular structure undergo electrophilic lactonization more readily [5] than unsaturated carboxylic acids with a flexible linear structure. It was established that of the two isomers of the unsaturated acis of the endo- and exo-norbornene (LVIII, n = 1) and 5-bi-cyclo[2.2.2]octene (LVIII, n = 2) series, only the endo isomers lead to the formation of γ-lactones. This property is used for the preparative separation of isomers or the establishment of their ratio in the mixture. The iodolactonization of unsaturated acids is suitable for this. For example, acids LVIII give γ-lactones LXV as a result of iodination [131-142].

The reaction of acids LVIII with chlorine [143] and Chloramine-T [16], mercuric acetate in the presence of methyl acrylate [144, 145], and thallium acetate [146-148], benzeneselenyl (sulfenyl) chlorides [20, 76, 149, 150], and SCl_2 and S_2Cl_2 in the presence of triethylamine [151] gives the corresponding lactones LIX-LXIV.



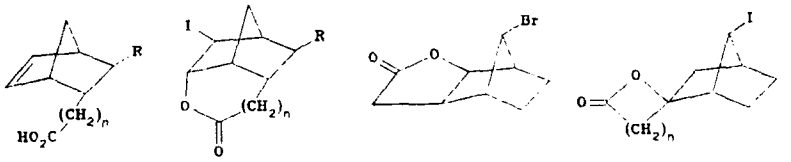
LIX $n=1,2$; LX R=H, CH_3; LXI R=H, CH_3, $n=1,2$; LXII R=$CH_2CH_2CO_2CH_3$; LXIII X=Tl(OAc)$_2$; LXIV X=PhSe(S), $n=1,2$; LXV R=H, OCH_3, R^1=H, CH_3, R^2=H, $CHCl_2$, $n=1,2$

The bromination of 7-trimethylsilylnorbornenoic acid (LXVI) with NBS in methyl alcohol [152] leads to a mixture of lactones LXVII (X = Br, R = NO_2) and dibromides LXIX (1:1). Lactone LXVII (R = CO_2CH_3, X = Br) was obtained in the bromination of LXVIb in $CHCl_3$ in 53% yield [153-155]. The lactonization of LXVIa upon reaction with Br_2, PhSeBr, and PhSCl gives a mixture of LXVII and LXVIII [155].



LXVI, LXVII a R=H, b R=CO_2CH_3, c R=NO_2; LXVII, LXVIII X=Br, PhSe, PhS

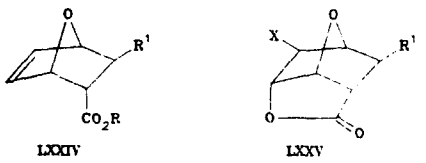
Upon iodination [156-158] and mercuration [157] acids LXX (n = 0, 1) are converted to the corresponding lactones LXXI (n = 0, 1). The bromination of LXX (R = H, n = 1) leads to lactone LXXII [157]. The iodolactonization [159, 160] of LXX (R = H, n = 2, 3) gives spirolactones LXXIII.



LXX LXXI LXXII LXXIII

LXX, LXXI R=H,Me,Ph, n=0,1; LXXIII n=2,3

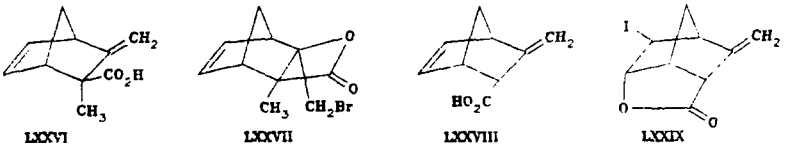
The bromination [161-164] of endo-7-oxabicyclo[2.2.1]-5-heptene-2-carboxylic acids LXXIVa, b and the iodination [165] of LXXIVc give the corresponding tricyclic lactones LXXV.



LXXIV LXXV

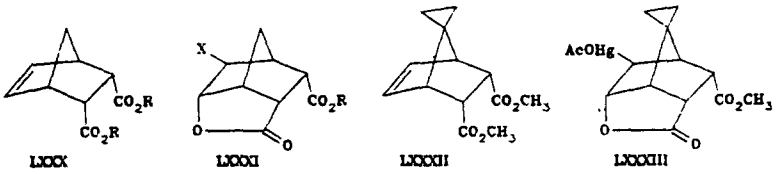
LXXIVa R=R¹=H, b R=H, R¹=CO_2H, c R=CH_3, R¹=H; LXXV X=Br, I

As a result of bromination, 3-methylenebicyclo[2.2.1]-5-heptenecarboxylic acid LXXVI is converted to β-lactone LXXVII [166, 167], while the isomeric acid LXXVIII gives γ-lactone LXXIX [168].



LXXVI LXXVII LXXVIII LXXIX

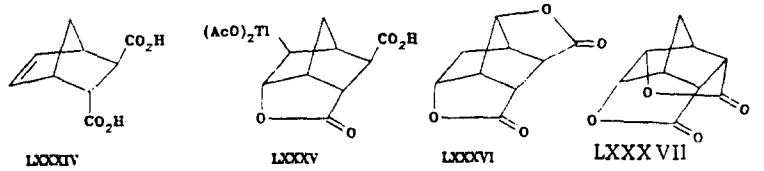
Ester LXXXa undergoes reaction with $Hg(OAc)_2$ with difficulty and gives lactones LXXXIa only in low yields [169, 170]. Acids LXXXb undergo the reaction more readily, and if an ester group and a carboxy group are present in the molecule, as, for example, in LXXXII, primarily the carboxy group undergoes reaction. Chlorolactone LXXXIb was obtained in almost quantitative yield when diester LXXXa was treated with chloro amines in the presence of SO_3 [171], as well as in the reaction with chlorine [143]. Lactone LXXXIc was obtained by the action of dialkylsulfenamides in the presence of SO_3 on diester LXXXa [172].



LXXX LXXXI LXXXII LXXXIII

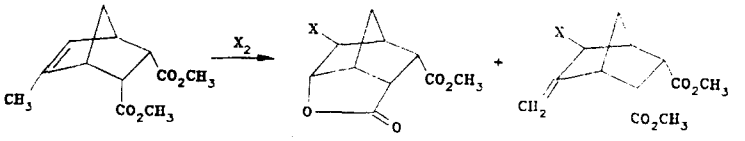
LXXX a R=CH_3, b R=H; LXXXI a–c R=CH_3, d R=H; a X=HgOAc, b X=Cl, c X=SAr, d X=$Tl(OAc)_2$

The reaction of LXXXb with $Tl(OAc)_3$ leads to the formation of LXXXId in 99% yield [146, 148], whereas 5-norbornene-trans-2,3-dicarboxylic acid (LXXXIV) under similar conditions gives lactone LXXXV. In contrast to $Tl(OAc)_3$, thallium trifluoroacetate reacts with acids LXXXIV and LXXXb to give, respectively, bilactones LXXXVI and LXXXVII [148]. Bilactone LXXXVII was also obtained as a result of the iodocyclization of the silver salt of 5-norbornene-cis-2,3-dicarboxylic acid (LXXXb) [51].



LXXXIV LXXXV LXXXVI LXXXVII

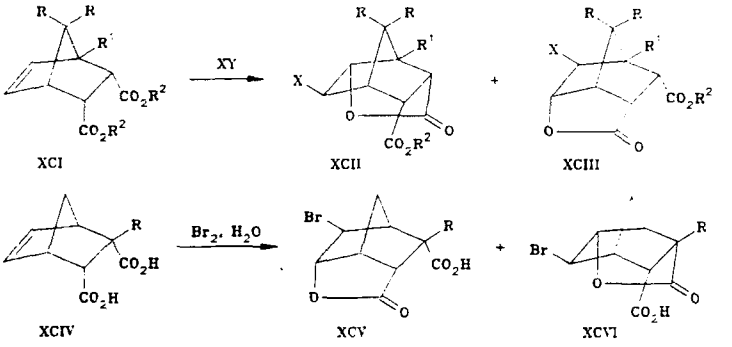
High regioselectivity of the reaction is observed in the halolactonization of 5-methyl-5-norbornenedicarboxylic acid ester LXXXVIII. γ-Lactones LXXXIXb, c were obtained in good yields in its bromination and iodination, whereas its chlorination and phenylsulfenylchlorination lead to the formation of mixtures of lactones LXXXIXa, d and diester XC in ratios of 73:23 and 46:54, respectively [173].



LXXXVIII LXXXIX XC

LXXXIX, XC a X=Cl, bX=Br, cX=I, d X=SPh

The halo- and sulfenolactonization of substituted norbornene acids and their methyl esters XCI give mixtures of lactones XCII and XCIII [173-175]. Lactones XCV and XCVI were obtained in the bromination of acid XCIV. It was shown that primarily the carboxy group attached to the more substituted carbon atom participates in the reaction at pH 3, as a result of which lactone XCVI is formed. Primarily lactone XCV is formed at pH 8 [176].

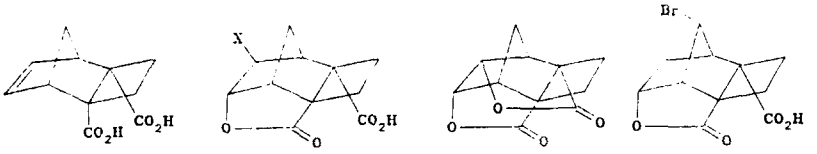


XCI XCII XCIII

XCIV XCV XCVI

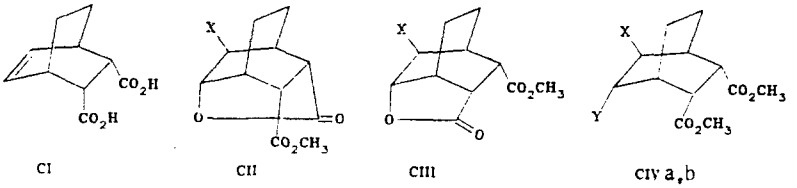
XCI R=CH_2—CH_2, H, CH_3, R^1=CH_3, C_2H_5, R^2=H, CH_3, XCII, XCIII X=Cl, Br, I, CH_3S, PhS, 2,4-$(NO_2)C_6H_3S$

Upon bromination and iodination, endo-dicarboxylic acid XCVII gives lactones XCVIII, which are converted to bilactone XCIX under the influence of alkali. The corresponding exo-dicarboxylic acid upon bromination undergoes isomerization with the formation of endo-bromolactone C.



XCVII XCVIII X=Br,I XCIX C

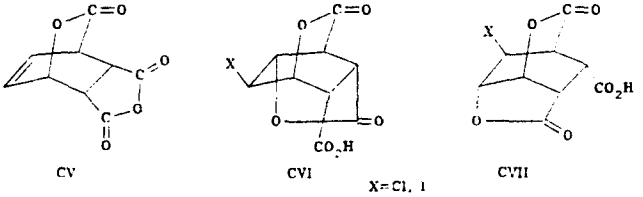
The reaction of electrophiles with endo-endo-5-bicyclo[2.2.2]octene-2,3-dicarboxylic acid (CI) dimethyl ester leads to the formation of a mixture of δ-lactone CII, δ-lactone CIII, and the 1,2 adduct of the addition of the electrophilic agent to the double bond (CIV) [178]. The reaction is highly stereoselective. In the case of the dimethyl ester of exo-endo-5-bicyclo[2.2.2]octene-2,3-dicarboxylic acid only the endo isomer participates in the lactonization reaction [179].



CI CII CIII CIV a,b

CII, CIII X=Cl, Br, I, ArSe(S); CIV a X=Y=Cl, Br, b X=PhSe, Y=Cl

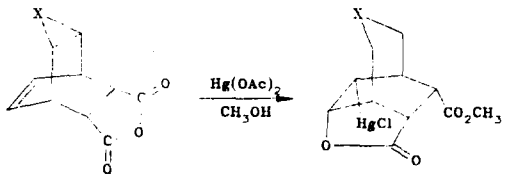
The halolactonization of the endo adduct of 2-pyrone with maleic anhydride (CV) under the influence of iodine and chlorine in water [180] leads to the formation of γ-lactone CVI or CVII. Upon chlorination under the indicated conditions the exo adduct gives a chlorohydrin, whereas it does not react with iodine.



CV CVI CVII

X=Cl, I

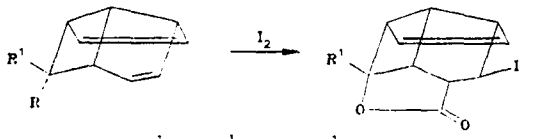
As a result of acetomercuration in the presence of NaCl in methanol, polycyclic anhydrides CVIIIa, b are converted to γ-lactones CIXa, b [181].



CVIII CIX

a X=CH_2, b X= -CH=CH-

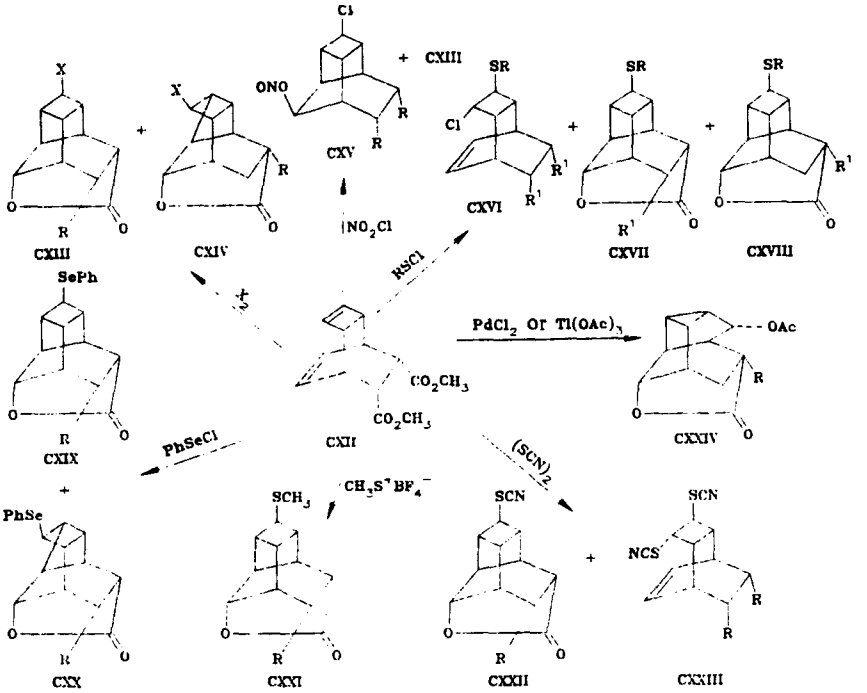
Iodolactonization has been successfully used to separate mixtures of epimeric acids CXa, b [182]. Lactone CXI gives only acid CXb.



a R=H, R'=CO_2H, b R=CO_2H, R'=H

Tricyclo[4.2.2.$0^{2,5}$]deca-3,7-diene-9,10-cis-endo-dicarboxylic acid and its methyl ester (CXII) are convenient models for the study of electrophilic lactonization. The spatial adjacency of the multiple bonds and the presence of carboxy or carboxymethyl groups as substituents in the molecule often lead to transannular cross cyclization in the reaction with electrophiles with the subsequent formation of γ- and δ-lactone rings.

The formation of the corresponding γ-lactones CXIV, CXVIII, and CXXIV, in addition to other products, was established in the halogenation [180, 182-186], arylsulfenylchlorination [188], and palladization and thallization with palladium and thallium salts [189, 190] of dimethyl ester CXII [183-191].



CXIII, CXIV R=CO_2CH_3, X=Cl, Br, I; CXV, CXIX—CXXIV R=CO_2CH_3; CXVI—CXVIII R=CH_3, C_6H_5, 2-NO_2—C_6H_4, 2,4-NO_2—C_6H_3, R'=CO_2CH_3

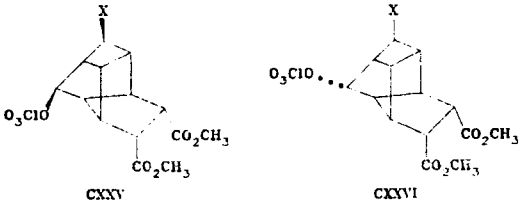
In 1978 authors from different countries in a study of the structures of the products of the arylsulfenylhalogenation [192, 193] and bromination [194] of diene CXII on the basis of the results of x-ray diffraction analysis demonstrated that the products are not γ-lactones but rather δ-lactones. The primary formation of δ-lactones in these reactions is evidently associated with the smaller degree of strain of the six-membered ring of the δ-lactones [195] as compared with γ-lactones.

The trans adducts involving the cyclobutene double bond are primarily formed in the reaction of arenesulfenyl halides with diester CXII in nonpolar media (CCl_4 or CH_2Cl_2). The yield of polycyclic lactones CXVII and CXVIII is only 7-8% [196, 197]. The yields of lactones increase sharply in polar solvents (CH_3COOH, CH_3CN) [195]. The formation of only δ-lactones CXVII is observed when the reaction of arenesulfenyl chlorides with diene CXII is carried out in the presence of salt additives under "doping-addition" conditions [195, 198]. Under these conditions a δ-lactone (CXVII, R = CH_3) is formed along with other products. The very same δ-lactone was obtained in the reaction of diene XCII with methanesulfenyl tetrafluoroborate CXXI [195].

Mercury salts do not give lactones on reaction with diester CXII; only products of direct and mixed addition of the electrophile to the cyclobutene double bond are formed [181]. The reaction of dithiocyanogen with diene CXII leads to a mixture of products of lactonization (CXXII) and addition (CXXIII) in a ratio of 44:27 [194]. The bromination of diester CXII in acetic acid and chloroform at room temperature gives a δ-lactone (CXIII, X = Br). An increase in the reaction temperature leads to the formation of a mixture of the lactone and the cis adduct of addition of bromine to the double bond [194]. A γ-lactone (CXIV, X = Cl) was obtained as a result of chlorination of diester CXII [183]. The reaction of CXII with chloro amines in the presence of SO_3 [171] leads to a mixture of chlorolactones CXIII and CXIV in a ratio of 1.5:1. The concerted addition of NO_2Cl to diene CXII is accompanied by the formation of a δ-lactone (CXIII, X = Cl, 56% yield) and chloro nitrate CXV (in 39% yield) [199].

Perchlorates CXXV and CXXVI were obtained in a study of the reaction of halogens and 2-nitro- and 2,4-dinitrobenzenesulfenyl chlorides with diene CXII in ether and CH_2Cl_2 in the presence of a large amount of lithium perchlorate; other products were lactones CXIII (X = Cl, Br) and CXVII [R = 2-$NO_2C_6H_4$, 2,4-$(NO_2)_2C_6H_3$] [200, 201].

The reaction of diester CXII with PhSeCl leads to the formation of regioisomeric δ-lactones CIX and CXX [178, 202].



CXXV CXXVI

The formation of substituted oxazolidines and oxazinones as a result of the electrophilic heterocyclization of unsaturated amino acids and urethanes proceeds in the same way as the formation of lactones in the electrophilic lactonization of unsaturated carboxylic acids [203-216]. However, an examination of these studies within the framework of this review is not possible.

It follows from the data presented above that the electrophilic lactonization of unsaturated carboxylic acids and their derivatives is distinguished by high regio- and stereoselectivity. The regioselectivity of the reaction is determined primarily by Markownikoff's rule, as well as by the nature of the solvent, which affects the state of the ion-pair equilibria of the electrophiles in solution. The ion-pair state of the electrophile also affects the stereoselectivity of lactonization along with the effect of the substituents in the carbon chain of the acid on its conformational state. The temperature also affects the regio- and stereoselectivity of electrophilic lactonization. Depending on the reaction temperature, the composition of the reaction products can be controlled kinetically or thermodynamically. Primarily γ- and δ-lactones are formed as a result of electrophilic lactonization.

A knowledge of the factors that affect the regio- and stereoselectivity of the electrophilic lactonization of unsaturated carboxylic acids makes it possible to predict the synthesis of lactones with a predesignated structure — precursors of diverse macrolides and polyester natural compounds.

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HETEROCYCLIZATION OF 1-ACETOXY-4-HALO-SUBSTITUTED 2-BUTENES IN THE PRESENCE OF ALKALI

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The reaction of 1-acetoxy-4-halo-substituted 2-butenes with potassium hydroxide was studied. It was established that trans-1,4-haloacetates form α-oxides of 1,3-dienes, whereas the corresponding cis isomers form 2,5-dihydrofuran derivatives. It was observed that the acetyl group in these compounds facilitates, as compared with halovinylhydrins, the formation of the corresponding heterocycles under the conditions described.

In the series of methods that are widely used to obtain oxides of 1,3-dienes the most universal is cleavage of vicinal halohydrins and their esters by bases [1, 2]. Results, according to which oxiranes of this type can be obtained from halohydrins that contain a vinyl fragment [3] and their esters [4], has become a substantial supplement to this method. We observed the latter reaction [4] in the course of establishing the configuration of the double bond in 4-acetoxy-1-bromo-2-methyl-2-butene (Id), which was obtained in the reaction of 2-methyl-3,4-epoxy-1-butene with acetyl bromide [5]. One should have expected that the action of alkali on the cis isomer of bromoacetate Id, which has an orientation of the functional groups that is favorable for the reaction, would lead to 3-methyl-2,5-dihydrofuran, whereas the trans isomer would be converted to the corresponding bromohydrin. Carrying out the reaction in the presence of dry potassium hydroxide led to an unexpected result — the only reaction product was isoprene oxide (IIb), i.e., intramolecular γ-allylic substitution occurred under the conditions of the S_N2 reaction [6]. Both the cis and trans form of bromoacetate Id can participate in this transformation, in view of which it became necessary to study the behavior of the individual stereoisomers in this reaction, and the possibility of extending it to other molecules that have a similar carbon skeleton also arose.

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