CHEMISTRY OF $\Delta^{\beta,\gamma}$-BUTENOLIDES (REVIEW)

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Data on methods of synthesis and on the chemical transformations of $\Delta^{\beta,\gamma}$-butenolides are correlated and systematized. Information on their biological activity is also presented.

Unsaturated five-membered lactones have been the subject of unflagging interest for researchers. This interest is due to the existence of the antibiotic, bactericidal, cardiotonic, and relatively recently discovered anticancer activity displayed by such lactones. It has also been demonstrated that the antibiotic and bactericidal activity of a number of natural biologically active compounds (vitamin C, kavain, parasorbic acid, etc.) is due to the presence of unsaturated lactone rings in the molecules of these compounds [1]. In this connection numerous investigations devoted to the development of general methods for the synthesis of unsaturated γ-lactones, to the study of their chemical properties, to the isolation of individual representatives from plants, and to the establishment of their structures have been published.

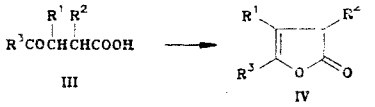
There are two types of unsaturated γ-lactones that differ with respect to the position of the double bond: $\Delta^{\alpha,\beta}$-butenolides [2(5H)-furanones] I and $\Delta^{\beta,\gamma}$-butenolides [2(3H)-furanones] II.

I II

The available review papers devoted to the chemistry of unsaturated lactones [2-4] have become noticeably obsolete. In the present review we attempted for the first time in the Soviet literature to correlate, analyze, and systematize data on the chemistry of $\Delta^{\beta,\gamma}$-butenolides, including recent research as well.

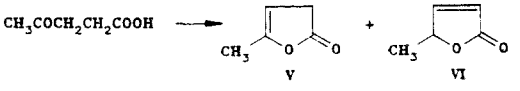
1. Methods for the Synthesis of $\Delta^{\beta,\gamma}$-Butenolides

1. From Keto Acids and Their Derivatives. One of the oldest known methods for the synthesis of $\Delta^{\beta,\gamma}$-butenolides is the intramolecular cyclization of carboxylic acids and their derivatives. Thus γ-keto acids III are converted to $\Delta^{\beta,\gamma}$-butenolides IV upon slow distillation [5-9].



III IV

One of the first representatives of $\Delta^{\beta,\gamma}$-butenolides is α-angelica lactone (V) [10-14], which was synthesized in 1885 from levulinic acid by precisely this method; the β form, viz., $\Delta^{\alpha,\beta}$-angelica lactone (VI), is formed simultaneously.



V VI

α-Angelica lactone is also obtained by heating levulinic acid with the addition of p-toluenesulfonic acid, ketene, or sulfuric acid [15-17], as well as by vacuum distillation [18]. The cyclization of levulinic acid proceeds readily when it is heated in the presence of acetic

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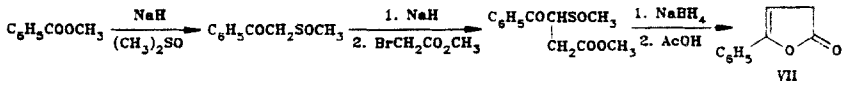
anhydride [19], acetyl chloride, or a mixture of acetic anhydride and a sulfonic acid [20, 21]. Aliphatic keto carboxylic acids undergo cyclization when they are heated with orthophosphoric acid [22], while aromatic keto acids undergo lactonization when they are heated with acetic anhydride [22-31] or acetyl chloride [19, 26, 32-34]. The lactonization of keto acids is also realized by heating to 300°C with subsequent distillation of the lactone at reduced pressure [35-39]. It has been established that many of them, particularly those with high melting points, are for the most part dimers rather than monomers [40].

Electron-donor substituents in the aromatic ring of β-aroylpropionic acids accelerate the reaction significantly. The ease of cyclodehydration also depends on the nature of the reagents used and decreases in the order $Ac_2O—H_2SO_4$ > AcCl > Ac_2O [41].

The synthesis of $\Delta^{\alpha,\beta}$- and $\Delta^{\beta,\gamma}$-butenolides from α-methyl-β-benzoyllactic acid by reduction with KBH_4 and dehydration in the presence of acetic anhydride was described in [41-43].

Esters of dibasic γ-keto acids readily undergo lactonization under the influence of concentrated phosphoric acid with the formation of substituted $\Delta^{\beta,\gamma}$-butenolides [44, 45].

A multistep synthesis of γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (VII) on the basis of methyl benzoate has been proposed [46].

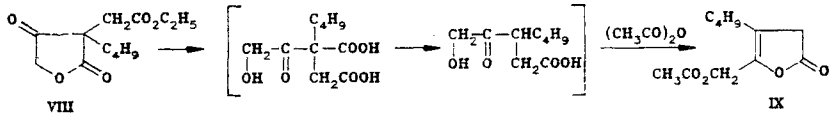


VII

Heating 4,7-dioxocaprylic acid with acetic anhydride leads to γ-(3-oxobutyl)-$\Delta^{\beta,\gamma}$-butenolide [47].

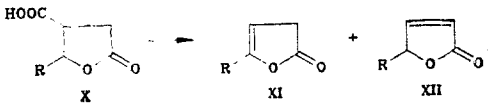
α-Acetyl-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide is formed in a mixture with a small amount of the $\Delta^{\alpha,\beta}$ isomer in the reaction of acetoacetate with ω-bromoacetophenone [47].

2. From Butyrolactone Derivatives. Butenolide IX was obtained by the hydrolysis and subsequent dehydration of α-carbethoxymethyl-β-oxobutyrolactone VIII [48].



VIII IX

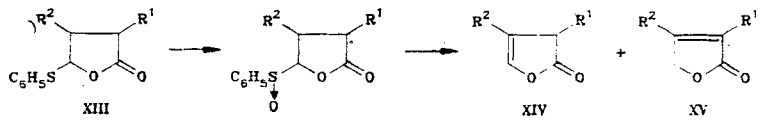
A method has been described for the synthesis of substituted $\Delta^{\beta,\gamma}$- and $\Delta^{\alpha,\beta}$-butenolides XI and XII by the reaction of alkyl- and phenylparaconic acids X with persulfates in the presence of catalytic amounts of silver and copper salts [49].



X XI XII

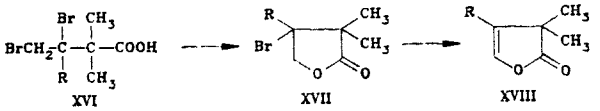
$\Delta^{\beta,\gamma}$-Butenolides were also obtained from hydroxylactones through the intermediate γ-keto acids [50-52].

$\Delta^{\beta,\gamma}$-Butenolides XIV are formed in mixtures with $\Delta^{\alpha,\beta}$-butenolides XV in the oxidation of 2,3-dialkyl(diaryl)-4-(phenylthio)butyrolactones XIII with m-chloroperbenzoic acid [53-55].



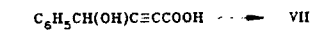
XIII XIV XV

3. From β,γ-Dibromo Acids. β,γ-Dibromo acids undergo hydrolysis and simultaneous dehydrobromination to give $\Delta^{\beta,\gamma}$-butenolides XI when they are refluxed with water or aqueous sodium carbonate solution [56-58]. Their thermal decomposition in the presence of quinoline leads to the same butenolides [59]. The intermediate β-bromobutyrolactones XVII, which are dehydrobrominated by the action of amines, were isolated in some cases [60, 61].



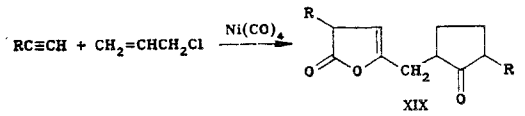
XVI XVII XVIII

4. From Acetylenic Compounds. The hydrogenation of acetylenic acids is a valuable method for the synthesis of $\Delta^{\beta,\gamma}$-butenolides. Thus the catalytic hydrogenation of 4-hydroxy-4-phenyl-2-butynoic acid at atmospheric pressure leads to phenylbutenolide VII [62].



When dipropargylmalonic acid and its esters are heated, they are converted to mixtures of α-propargyl-α-angelica lactone, α-propargyl-β-angelica lactone, and a bislactone [63-66].

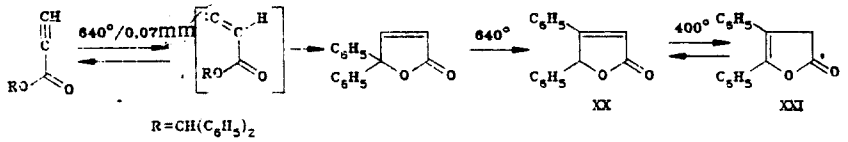
$\Delta^{\beta,\gamma}$-Butenolide derivatives XIX are obtained in the reaction of allyl halides with terminal alkynes in the presence of nickel tetracarbonyl [67, 68]. The reaction of an allyl halide with acetylene and carbon monoxide in the presence of nickel chloride and an alloy of manganese with iron is similar in character [69].



XIX

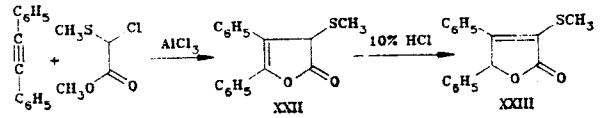
$\Delta^{\beta,\gamma}$-Butenolide derivatives are also formed in the reaction of carbon monoxide with ethylene and acetylene at 160°C and a pressure of 200 atm in the presence of palladium iodide [70].

The blitz-vacuum pyrolysis of diphenylmethyl propiolate leads to 4,5-diphenyl-2(3H)-furanone (XX) along with 2(5H)-furanone derivative XXI [71].



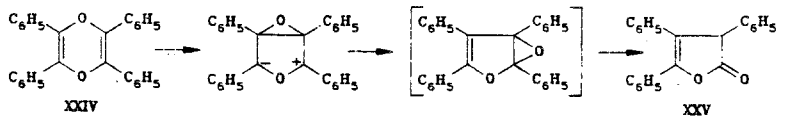
XX XXI

The [3+ + 2]-polar cycloaddition of an α-chloro-α-(methylthio)acetate to diphenylacetylene [72] in the presence of Lewis gives 2(3H)- and 2(5H)-furanone derivatives XXII and XXIII.



XXII XXIII

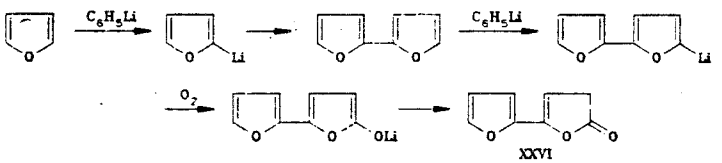
5. Rearrangements. Heating tetraphenyl-1,4-dioxine (XXIV) with acetic anhydride leads to tetraphenylbutenolide XXV [73]:



XXIV XXV

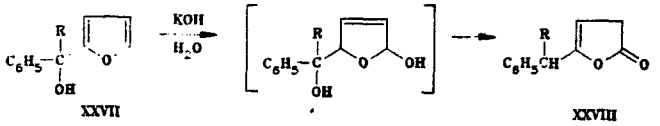
An interesting example of rearrangement is the formation of α,β,γ-triphenyl-α-benzoyl-$\Delta^{\beta,\gamma}$-butenolide in the oxidation of tetraphenylcyclopentadienone with chromium pentoxide [74].

6. From Furan and Its Derivatives. γ-(2-Furyl)-$\Delta^{\beta,\gamma}$-butenolide (XXVI) is formed in the reaction of furan with phenyllithium [75].



XXVI

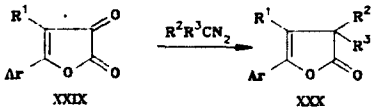
$\Delta^{\beta,\gamma}$-Butenolides XXVIII were obtained from alkyl- or arylfurylcarbinols XXVII in their reaction with water in the presence of bases [5].



XXVII XXVIII

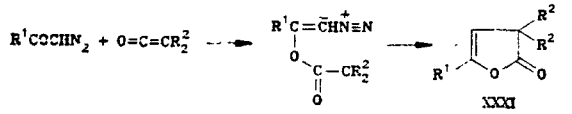
The oxidation of furfural and 5-methylfurfural with hydrogen peroxide leads to a mixture of the corresponding 2(3H)- and 2(5H)-furanones [76]. 2(3H)-Furanone derivatives are also obtained in the oxidation of 5-substituted 2-trimethylsilylfurans with peracetic acid [77].

5-Arylfuran-2,3-diones XXIX form $\Delta^{\beta,\gamma}$-butenolides XXX when they are refluxed with diazoalkanes in absolute benzene [78].



XXIX XXX

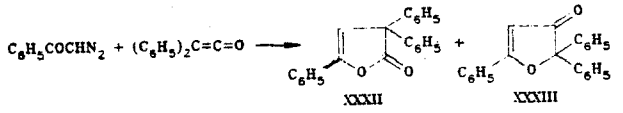
7. From Diazo Ketones and Ketenes. $\Delta^{\beta,\gamma}$-Butenolides XXXI are obtained by the reaction of diazo ketones with ketenes [79-86].



XXXI

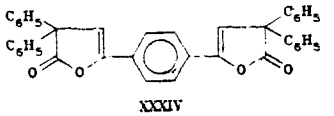
The thermolysis of α-diazo ketones also leads to $\Delta^{\beta,\gamma}$-butenolides [84-86].

Triphenyl-$\Delta^{\beta,\gamma}$-butenolide XXXII and 2,2,5-triphenyl-3(3H)-furanone (XXXIII) were obtained from α-diazoacetophenone and diphenylketene [87, 88].



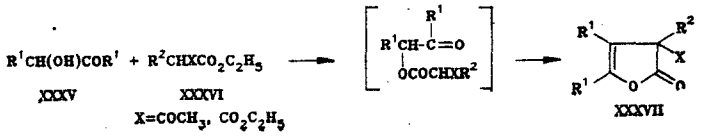
XXXII XXXIII

Bis-$\Delta^{\beta,\gamma}$-butenolides XXXIV were synthesized from the corresponding bis(diazo) ketones [80]. The synthesis of similar bisbutenolides from 2,5-diazoacetylthiophene was described in [83].



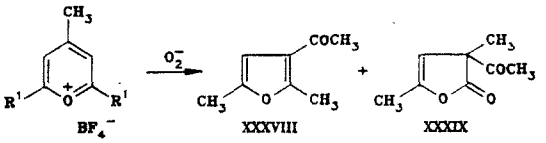
XXXIV

8. By the Reaction of Acyloins with Acetoacetic and Malonic Acid Esters. An interesting method for the synthesis of substituted $\Delta^{\beta,\gamma}$-butenolides XXXVII is the reaction of acyloins XXXV with alkylacetoacetic and alkylmalonic acid esters XXXVI in the presence of catalysts of basic character [89, 90]:

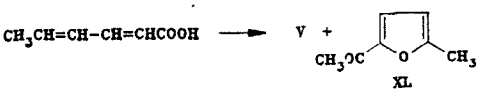


XXXV XXXVI X=$COCH_3$, $CO_2C_2H_5$ XXXVII

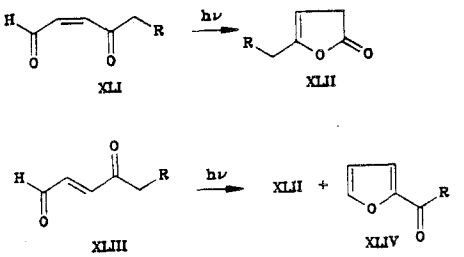
9. Other Methods of Synthesis. Pyrylium tetrafluoroborates react with O_2^- to form primarily mixtures of furan XXXVIII derivatives and 2(3H)-furanone XXXIX derivatives [91].



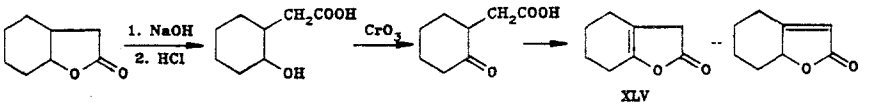
Sorbic acid in acidic aqueous solutions in the presence of excess SO_2 undergoes cyclization to give a mixture of α-angelica lactone (V) and 2-acetyl-5-methylfuran (XL) [92].



A difference in the behavior of the cis and trans isomers was noted in the photochemical production of 2(3H)-furanones from dicarbonyl compounds of the ethylene series [93]. Whereas exclusively 5-alkyl-2(3H)-furanone XLII is formed in irradiation of cis-isomer XLI, irradiation of trans-isomer XLIII under similar conditions leads to a mixture of XLII and alkyl furyl ketone XLIV.



10. Preparation of Condensed $\Delta^{\beta,\gamma}$-Butenolides. The synthesis of condensed $\Delta^{\beta,\gamma}$-butenolides XLV via the following scheme was described in [94, 95]:



Butenolides condensed with a cyclopentane ring were obtained by carbonylation of dienes over a palladium catalyst [96], while the condensation of resorcinol with α-hydroxy- or α-chlorophenylacetic acid nitriles leads to butenolides condensed with a benzene ring [97].

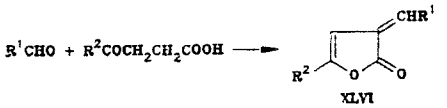
The synthesis of $\Delta^{\beta,\gamma}$-butenolides condensed with a benzene ring by refluxing hydroxynaphthalenes in benzene solution was described in [98].

α,α'-Dimethoxydihydropentofuran is hydrolyzed to give a mixture of $\Delta^{\alpha,\beta}$- and $\Delta^{\beta,\gamma}$-butenolides condensed with a cyclohexane ring in a ratio of 1:3 [99].

The synthesis of $\Delta^{\beta,\gamma}$-butenolides of the furoquinoline series, to which the alkaloids γ-fagarine, dictamnine, lunacrine, etc., belong, was described in [100].

A method for obtaining various benzofuran-2-ones from phenols and glyoxal in the presence of catalysts, viz., Lewis acids, a cation-exchange resin, and C_1–C_{12} organic acids, has been patented [101]. An interesting method has been developed for the synthesis of substituted benzo-2-furanones by the reaction of N-arylsulfonyl-1,4-benzoquinonimines with esters and arylamides of 3-alkyl(cycloalkyl)aminocrotonic acids and subsequent cyclization of the products [102].

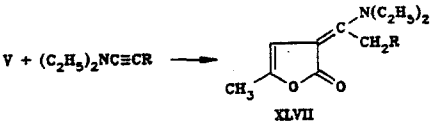
11. Syntheses of α-Arylidene(alkylidene)-γ-aryl(alkyl)-$\Delta^{\beta,\gamma}$-butenolides. From Keto Acids by Perkin–Erlenmeyer Condensation. The condensation of γ-keto acids with aldehydes in the presence of acetic anhydride and sodium acetate has been widely used as the principal method for the synthesis of α-arylidene(alkylidene)-γ-aryl(alkyl)-$\Delta^{\beta,\gamma}$-butenolides XLVI [103-120].



Cyclohexanone, fluorenone, isatin, and tetrachlorophthalic anhydride react with β-aroylpropionic acids under the conditions of the Perkin–Erlenmeyer reaction to give the corresponding butenolides [52, 121, 122]. Ketones do not undergo the normal Perkins–Erlenmeyer reaction, but acetone, methyl ethyl ketone, and 4-nitroacetophenone condense with β-aroylpropionic acids in the presence of potassium carbonate or sodium bicarbonate [2]. Two stereoisomers of α-(5-nitrofurylidene)-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide are formed in the condensation of 5-nitrofurfural with β-benzoylpropionic acid [105, 106]. Benzaldehyde also condenses with β-benzoylpropionic acid to give a mixture of stereoisomers; however, these isomers were not isolated in the individual state [123].

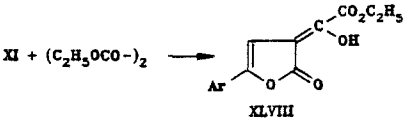
From $\Delta^{\beta,\gamma}$-Butenolides. The condensation of α-angelica lactone (V) and a number of $\Delta^{\beta,\gamma}$-butenolides with aromatic aldehydes and with 5-substituted furfurals leads to the corresponding α-arylidene-$\Delta^{\beta,\gamma}$-butenolides [124-131].

Diethylaminoethylidene derivatives XLVII were obtained from α-angelica lactone (V) and diethylaminoacetylenes [132-134].



XLVII

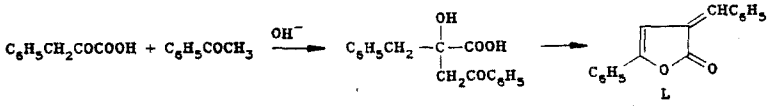
γ-Aryl-$\Delta^{\beta,\gamma}$-butenolides XI condense with diethyl oxalate in the presence of sodium ethoxide to give α-alkylidene-γ-aryl-$\Delta^{\beta,\gamma}$-butenolides XLVIII [135].



XLVIII

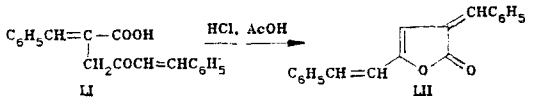
Aroylpropionic acid esters also react similarly with diethyl oxalate [135].

From Pyruvic Acid Derivatives. Phenylpyruvic acid condenses with acetophenone in the presence of bases to give α-hydroxy-α-phenacyl-β-phenylpropionic acid (XLIX), which undergoes cyclization to α-benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (L) on heating with a mixture of hydrochloric and acetic acids [136, 137]. Under similar conditions 4-methylacetophenone gives a mixture of stereoisomers [136-139].



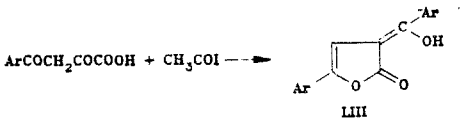
L

The product of the reaction of acetone and phenylpyruvic acid undergoes condensation with benzaldehyde and is converted to α,δ-dibenzylidenelevulinic acid (LI) and then to lactone LII [139].



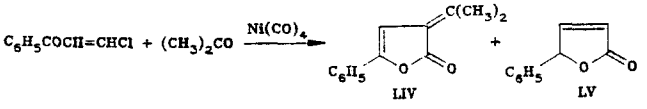
LI LII

Arylidenebutenolides LIII are formed from aroylpyruvic acids and acetyl iodide [140].



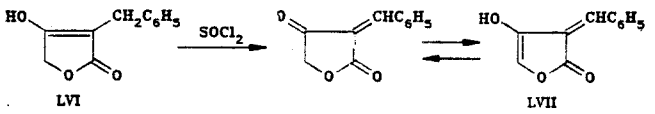
LIII

Other Methods of Synthesis. β-Chlorovinyl phenyl ketone reacts with acetone in the presence of nickel tetracarbonyl to give $\Delta^{\beta,\gamma}$-butenolide LIV and $\Delta^{\alpha,\beta}$-butenolide LV [141, 142].

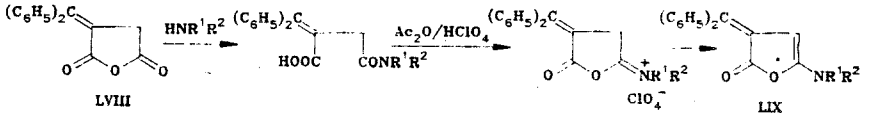


LIV LV

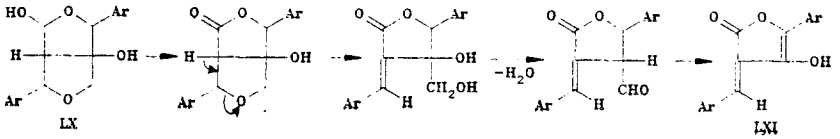
α-Benzyltetronic acids LVI react with thionyl chloride to give α-benzylidene-β-hydroxy-$\Delta^{\beta,\gamma}$-butenolides LVII through intermediate oxobutyrolactones [143].



(Diphenylmethylene)succinic anhydride (LVIII) reacts with amines through a series of intermediate transformations to give $\Delta^{\beta,\gamma}$-butenolides LIX [144].

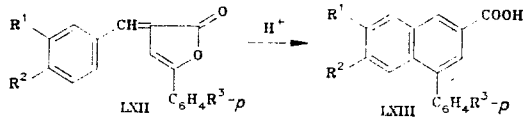


The reaction of gummadiol LX with 2,3-dichloro-5,6-dicyanobenzoquinone leads to 2-arylidene-5-aryl-2(3H)-furanones LXI [145]:



2. Chemical Properties of $\Delta^{\beta,\gamma}$-Butenolides

$\Delta^{\beta,\gamma}$-Butenolides have high reactivities and behave basically like cyclic esters in chemical transformations. They form γ-keto acids in alkaline or acidic hydrolysis [146-148]. However, the reaction of α-arylidene-γ-arylbutenolides LXII with hydrochloric and acetic acids leads to naphthoic acid derivatives LXIII [149, 150].

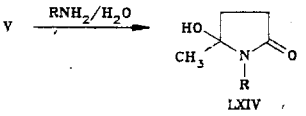


α-Arylidene-β-aryl-$\Delta^{\beta,\gamma}$-butenolides give α-phenylcinnamic derivatives [151].

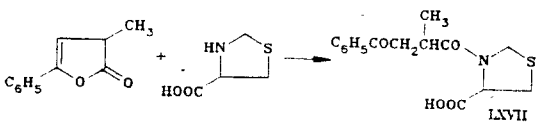
Thionyl chloride and thionyl bromide convert lactone V to a halo carboxylic acid halide [152]. Lactone V also reacts with an alcohol solution of hydrogen chloride to give ethyl levulinate [94], whereas an α-phenacylcinnamic acid ester is obtained in the alcoholysis of L [94].

The reaction of $\Delta^{\beta,\gamma}$-butenolides with ammonia and amines proceeds with the formation of the corresponding amides, which undergo cyclization in the presence of acidic or basic agents to lactams – pyrrolinones [10, 22-25, 34, 153-166].

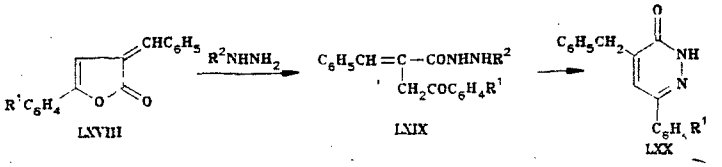
Compound V reacts with aqueous solutions of some primary amines to give 5-hydroxypyrrolidone derivatives LXIV [154, 167].



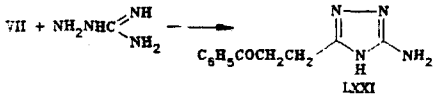
3-Methyl-5-phenyl-2(3H)-furanone (LXV) reacts with L-thiazolidine-4-carboxylic acid (LXVI) with ring opening to give propionylthiazolidine derivatives LXVII [168].



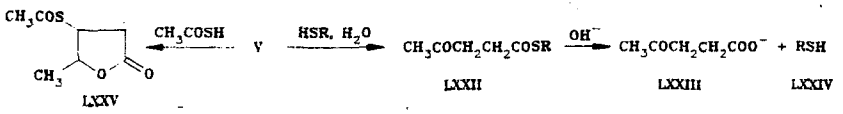
$\Delta^{\beta,\gamma}$-Butenolides react with hydroxylamine and hydrazine to give hydroxamic acids and hydrazides. Under the influence of hydrazine, lactone V is converted to levulinic acid hydrazide, whereas it reacts with phenylhydrazine to give levulinic acid phenylhydrazide phenylhydrazone [169]. α-Benzylidene-γ-aryl-$\Delta^{\beta,\gamma}$-butenolides LXVII react with hydrazine hydrate and phenylhydrazine to give α-phenacylcinnamic acid hydrazides LXIX [3], which in the presence of acidic agents undergo cyclization to pyridazinones LXX [163-165, 170, 171].



5-Phenyl-2(3H)-furanone (VII) reacts with aminoguanidine with ring opening to give 2-substituted 5-amino-1,2,4-triazole LXXI [172].

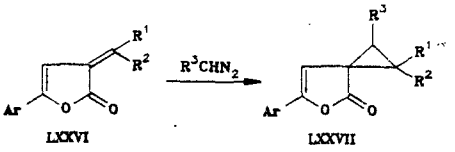


Compound V reacts with thioglycolic acid in aqueous solution with opening of the lactone ring to give, initially, thiolevulinic acid ester LXXII and then levulinate ion (LXXIII) and thioglycolic acid (LXXIV) [173]. The reaction of lactone V with thioacetic acid leads to the lactone (LXXV) of cis-3-acetylthio-4-hydroxyvaleric acid [174].

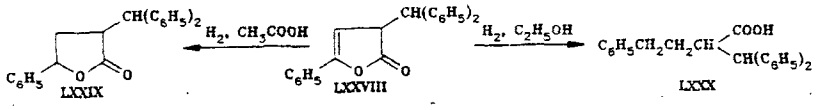


The reaction of V with diazamethane at 0°C in the presence of alcohols has been used to obtain alkyl levulinates [175]. If there is a hydroxy or carboxy group in the butenolide ring, the corresponding methoxy or carbomethoxy derivatives are formed [176-178].

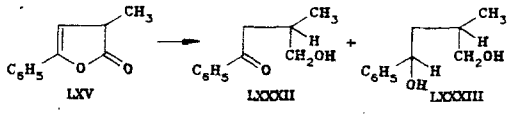
The reaction of α-arylidene(cyclohexylidene)-γ-aryl-$\Delta^{\beta,\gamma}$-butenolides LXXVI with diazoalkanes leads to cyclopropane derivatives LXXVII [179, 180].

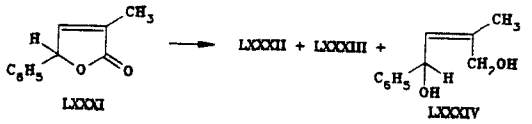


A systematic study of the hydrogenation of butenolides showed that $\Delta^{\beta,\gamma}$-butenolides usually form desoxy acids, whereas $\Delta^{\alpha,\beta}$-butenolides give valerolactone derivatives [181, 182]. However, mixtures of desoxy acids and valerolactone derivatives were obtained from β-substituted $\Delta^{\beta,\gamma}$-butenolides. α-Benzylidene-butenolides L are reduced by zinc and acid to α-benzyl-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide [183]. Upon reduction with hydrogen (with palladium on carbon as the catalyst) in acetic acid α-benzhydryl-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (LXXVIII) is converted to lactone LXXIX, whereas it is converted to acid LXXX in alcohol [184].

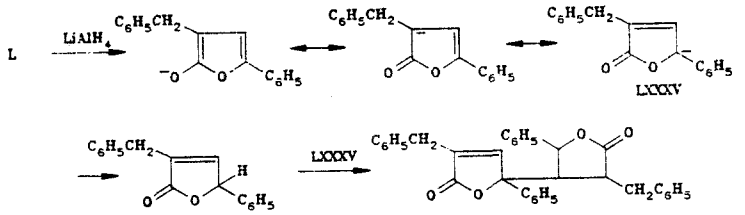


The reaction of butenolides with complex metal hydrides has been described in a number of papers [185-189]. Lactone V reacts with lithium aluminum hydride in N-ethylmorpholine at 90°C to give 3-acetylpropanol [186]. The reduction of isomers LXV and LXXXI was studied to compare the properties of $\Delta^{\alpha,\beta}$- and $\Delta^{\beta,\gamma}$-butenolides. It was established that $\Delta^{\beta,\gamma}$-butenolide LXV forms keto alcohol LXXXII and saturated diol LXXXIII, while $\Delta^{\alpha,\beta}$-butenolide LXXXI forms, in addition to the same compounds, unsaturated diol LXXXIV [188, 189].



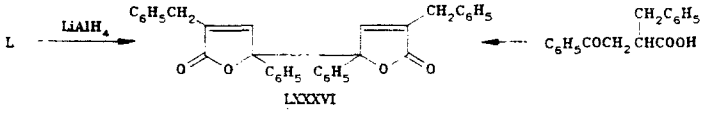


In earlier papers it was reported that the principal product of the reduction of α-benzylidenebutenolide L is α-benzyl-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide if the reaction is carried out in ether or tetrahydrofuran with a twofold excess of lithium aluminum hydride [2]. However, further study showed that the product is a dimer. The following mechanism of this interesting transformation is proposed [185]:



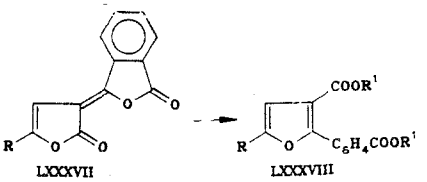
Similar dimers were also obtained from o-chloro-, p-chloro-, o-methoxy-, and p-methoxybenzylidene analogs of butenolide L [185].

Bislactone LXXXV, which is also obtained by cyclization of β-benzoyl-α-benzylpropionic acid by the action of acetic anhydride, is formed in 20% yield in the reduction of L with lithium aluminum hydride at −25°C [185].

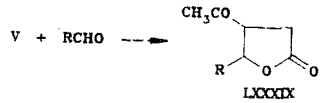


Compounds VII and V behave like acylating agents with respect to indolylmagnesium iodide and form the corresponding acylindoles [190]. α-Benzylidenebutenolide L reacts with excess phenylmagnesium bromide to give 1,4-addition product LXXVIII [184]; in addition, α-benzhydryl-γ-phenyl-$\Delta^{\alpha,\beta}$-butenolide is also formed in small amounts [184, 191]. The reaction with methylmagnesium iodide proceeds similarly [191].

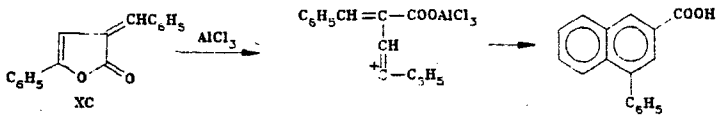
Butenolides can be readily converted to furan derivatives. Thus carboxyfuran derivatives LXXXVIII were obtained from butenolides LXXXVII by treatment with methanol–sulfuric acid (10:1) [192].



Lactone V undergoes aldol condensation with aromatic and heterocyclic aldehydes in the presence of boron trifluoride etherate to give acetyldihydrofuranone derivatives LXXXIX, which are used as sedative and cardiovascular agents [193, 194].



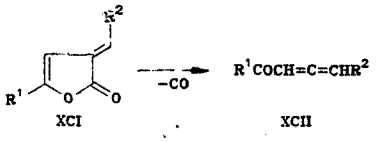
α-Arylidenebutenolides XC undergo intramolecular alkylation in the presence of anhydrous $AlCl_3$ [191, 195, 196]. The reaction evidently proceeds through electrophilic attack in the ortho position of the intermediate carbonium ion [195]. In addition to the principal product, side products, the structures of which depend primarily on the nature of the arylidene part, are also obtained in [197].



XC

α-Angelica lactone (V) is cleaved by the action of $NaIO_4$–OsO_4, while β-angelica lactone (VI) remains unchanged under similar conditions [198].

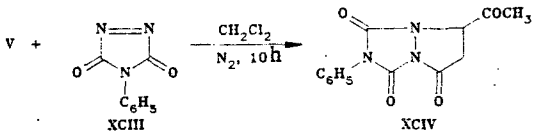
In the case of blitz-vacuum pyrolysis, trans-α-arylidene-γ-alkyl(aryl)-$\Delta^{\beta,\gamma}$-butenolides XCI form allene derivatives XCII [199].



XCI XCII

The aminomethylation of γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide led to the corresponding α-(dialkylaminomethylidene) derivative [200].

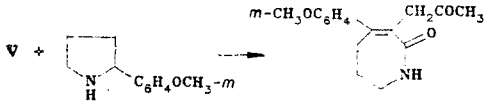
The addition of lactone V to 4-phenyl-1,2,4-triazoline-3,5-dione (XCIII) leads to a compound (XCIV) with two condensed heterorings [201].



XCIII XCIV

5-Hydroxymethyl-2(3H)-furanone undergoes thermal rearrangement to 2H-pyrone [202].

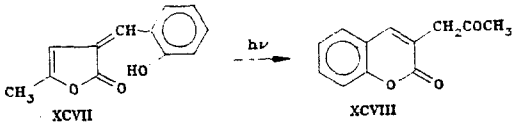
The reaction of V with 2-(3-methoxyphenyl)-1-pyrrolidine (XCV) leads to a new heterocycle — 3-acetonyl-4-(3-methoxyphenyl)-1.5,6,7-tetrahydro-2H-azepinone (XCVI) [203].



XCVI

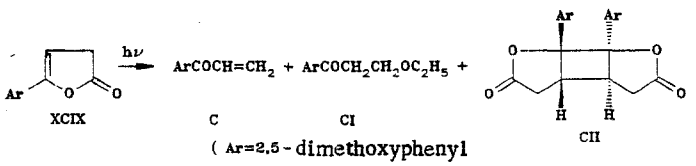
The photochemistry of $\Delta^{\beta,\gamma}$-butenolides has undergone great development in recent years. In the case of UV irradiation of lactone V and α,β-dimethyl- and α-phenyl-$\Delta^{\beta,\gamma}$-butenolides they undergo photodecarboxylation with the formation of, respectively, methyl vinyl, methyl propenyl, and phenyl vinyl ketones [204-206].

α-Benzylidenebutenolide L undergoes two types of primary photochemical transformations: detachment of a proton from the solvent and geometrical isomerization. In the case of illumination with light with a wavelength of 3650 Å the starting compound, which is a mixture of isomers, is converted completely to the cis isomer [207]. Similarly, α-(o-hydroxybenzylidene)-γ-methyl-$\Delta^{\beta,\gamma}$-butenolide (XCVII) undergoes photochemical isomerization to the cis isomer; further irradiation gives 3-acetonylcoumarin (XCVIII), which is the product of intramolecular acylation [208].



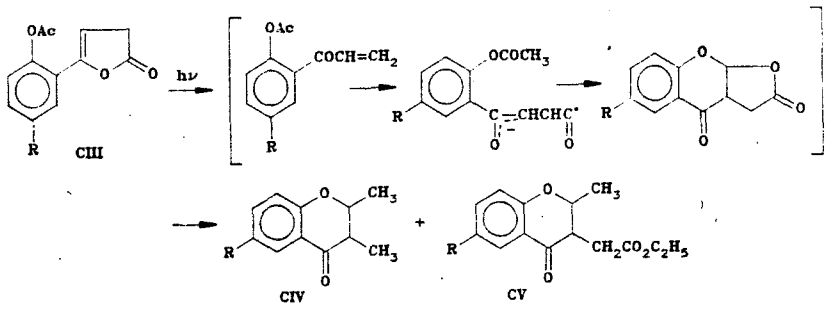
XCVII XCVIII

γ-Phenyl-$\Delta^{\beta,\gamma}$-butenolide derivatives that contain CH_3O and CH_3COO groups in the benzene ring (XCIX and CIII) form mixtures of products (C-CII and CIV, CV) upon irradiation [206].

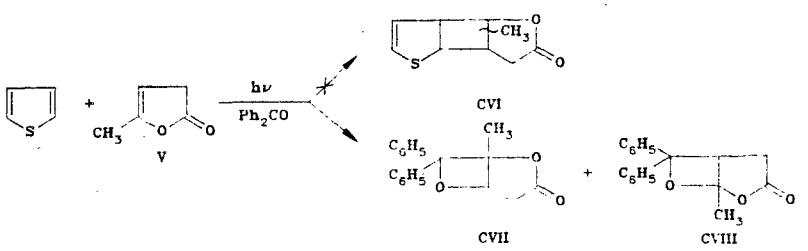


XCIX C CI CII

(Ar=2.5-dimethoxyphenyl



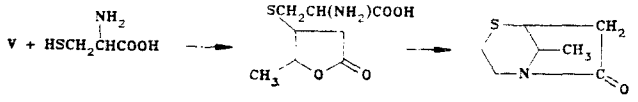
Instead of the expected [2 + 2]-cycloaddition product CVI, a mixture of derivatives of isomeric oxetanes CVII and CVIII is formed in the irradiation of a mixture of lactone V and thiophene in benzophenone [209].



3. Biological Activity

Most compounds of both natural and synthetic origin that contain lactone rings have a broad spectrum of biological activity; this is due precisely to the presence of unsaturated lactone rings. Hydrogenation of the double bond and hydrolysis of the lactone ring lead to the loss of biological activity.

Both angelica lactones have bactericidal properties [210]. The antibiotic activity of unsaturated lactones is explained by their ability to react with cysteine, as well as with enzymes that contain sulfhydryl groups and are of great significance for the vital activity of microorganisms [211, 212]. It is assumed that the bactericidal activity of unsaturated lactones is associated with the ability of the unsaturated bond of the lactone to add SH groups, which are present in bacterial proteins, thereby retarding processes associated with the growth of bacteria. The reaction of cysteine with some unsaturated lactones, particularly with angelica lactones, has been specially studied [211, 212]. The reaction proceeds via the scheme



Data relative to the anticancer activity of $\Delta^{\beta,\gamma}$-butenolides have been obtained in recent years. According to data from the National Cander Institute of the USA, α-angelica lactone inhibits 7,12-dimethylbenzanthracene- or benzopyrene-induced neoplasia of the mammary glands and rumina of rats and mice [213, 214]. In addition, α-angelica lactone (V) increases the inhibiting capacity of an enzyme, viz., glutathione-S-transferase, relative to neoplasia [215-217].

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FIVE-MEMBERED 2,3-DIOXOHETEROCYCLES

3.* THE REACTION OF 5-ARYL-2,3-DIHYDROFURAN-2,3-DIONES WITH ALIPHATIC AND AROMATIC NITRILES

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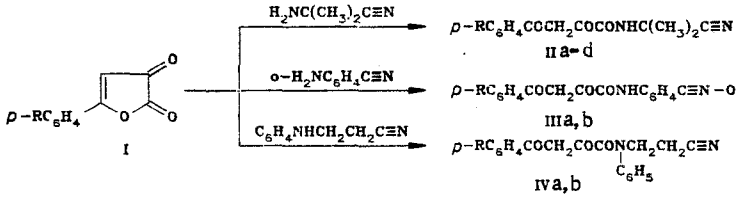
On reaction of 5-aryl-2,3-dihydrofuran-2,3-diones with α-aminoisobutyronitrile, o-aminobenzonitrile, and β-anilinopropiononitrile, we obtained aroylpyruvic acid N-(1-methyl-1-cyanoethyl)-, N-(o-cyanophenyl)-, and N-phenyl-N-(cyanoethyl)-amides, respectively. On reaction of 5-aryl-2,3-dihydrofuran-2,3-diones with cyanoacetamide we obtained aroylacetic acid N-(cyanoacetyl)amides, while in the case of methyleneaminoacetonitrile and p-dimethylaminobenzonitrile we obtained (6-aryl-4-oxo-2,3-dihydro-1,3-oxazin-3-yl)acetonitriles and 2-(p-dimethylaminophenyl)-6-aryl-1,3-oxazine-4-ones, respectively.

Earlier it was noted that aroylketenes generated by thermolysis of 5-aryl-2,3-dihydrofuran-2,3-diones (I) do not react in a $(4\pi + 2\pi)$-cycloaddition with aliphatic and aromatic nitriles but react with N,N-disubstituted-N-cyanoamines, forming 2-amino-6-aryl-1,3-oxazin-4-ones [2,3]. If the C≡N group in the reagent is directly linked with a primary or secondary amino group, then ring opening of compound I proceeds with the formation of aroylpyruvic acid N-cyanoamides, accompanied by the addition of α-enolic hydroxyl to C≡N, and 2-imino-5-phenacylidene-4-oxazolidones appear as reaction products [4, 5]. In connection with this, it was of interest to react aminonitriles which contained unlinked amino and cyano groups with compounds I. Among such reagents we used α-aminoisobutyronitrile, o-aminobenzonitrile, β-anilinopropionitrile, cyanoacetic acid amides, and p-dimethylaminobenzonitrile.

On investigation of the interaction of compound I with α-aminobutyronitrile, 0-aminobenzonitrile, and β-anilinopropiononitrile, it was established that, due to nucleophilic attack of the amino group on the lactone carbonyl of compound I, furan ring opening ensues and the products of reaction are, respectively, N-(1-methyl-1-cyanoethyl)-(IIa,d), N-(o-cyanophenyl)-(IIIa,b), and N-phenyl-N-(cyanoethyl)-(IVa,b) arolypyruvic acid amides.



I—IV a R=H, b R=CH_3; II c R=C_2H_5O, d R=Br

*For Communication 2, see [1].

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