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The Chemistry of $\Delta^{\alpha\beta}$-Butenolides†

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Data on the chemistry of $\Delta^{\alpha\beta}$-butenolides are surveyed and described systematically and the available information in the literature about the methods of preparation of these compounds are discussed. The chemical reactions of $\Delta^{\alpha\beta}$-butenolides are examined and a brief account is given of the biological activity of unsaturated γ-lactones.
The bibliography includes 253 references.

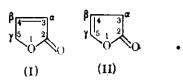
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I. INTRODUCTION

There has been a growth of interest in the simplest unsaturated γ-lactones after the discovery of the antibiotic properties of many natural products—protoanemonin, clavacin, penicilloic acid, vitamin C, and others. They all exhibit their antibiotic activity in combination with strong bactericidal properties [1,2]. Numerous investigations have shown that the unusual specific action of these antibiotics is determined mainly by the presence of the unsaturated γ-lactone ring and also by the nature and positions of the functional groups present. The unsaturated γ-lactone ring is also encountered in many other biologically active compounds [3-6]. Fairly extensive experimental data have now accumulated on the synthesis and reactions of unsaturated γ-lactones. These studies have demonstrated the possibility of the wide-scale employment of γ-lactones in various branches of the national economy and also in organic synthesis.

$\alpha\beta$-Unsaturated γ-lactones (I) and $\beta\gamma$-unsaturated γ-lactones (II) are distinguished on the basis of the position of the double bond and chemical properties:



(I) (II)

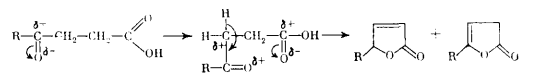
This review is a first attempt in the Soviet scientific literature at a survey and a systematic account of data on the chemistry of $\Delta^{\alpha\beta}$-butenolides published up to 1976.

II. METHODS OF SYNTHESIS OF $\Delta^{\alpha\beta}$-BUTENOLIDES

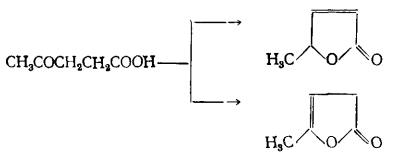
The available literature data on the methods of preparation of $\Delta^{\alpha\beta}$-butenolides can be in the main subdivided into several groups.

1. The Preparation of $\Delta^{\alpha\beta}$-Butenolides from Ketoacids and Their Derivatives

One of the commonest methods of the synthesis of $\Delta^{\alpha\beta}$-butenolides involves the intramolecular cyclisation of various keto- and diketo-acids and their derivatives. In order to achieve such synthesis, it is necessary that the oxo- and carboxy-groups in these compounds are in the γ-position; it is also essential that the ketoacid should be capable of existing in the enolic form:

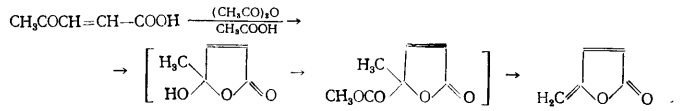


One of the first $\Delta\alpha\beta$-butenolides obtained was angelica lactone, synthesised as early as 1885 [7-12] from levulinic acid. On heating under atmospheric pressure, levulinic acid loses a water molecule and is converted into a mixture of two isomeric unsaturated $\Delta^{\alpha\beta}(\beta)$- and $\Delta^{\beta\gamma}(\alpha)$-angelica lactones:

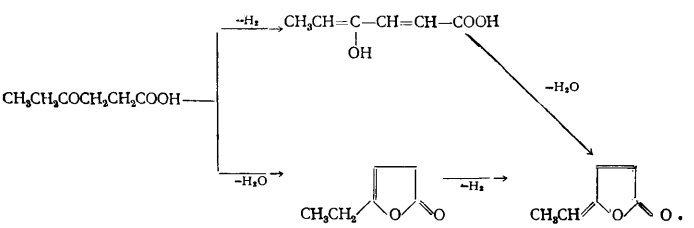


β-Angelica lactone is also obtained on heating levulinic acid with keten [13] (or with added toluene-*p*--sulphonic acid [14]) and on distillation of acetyl-levulinic acid [15].

When β-acetylacrylic acid is heated with a mixture of acetic anhydride and acetic acid in the presence of a small amount of concentrated sulphuric or toluene-*p*-sulphonic acid, γ-methylene-$\Delta^{\alpha\beta}$-butenolide (protonemonine) is obtained [16]:



Substituted protoanemonines have been obtained from levulinic acid homologues in the presence of complex catalysts [17]. The elimination of water and dehydrogenation can be carried out consecutively:



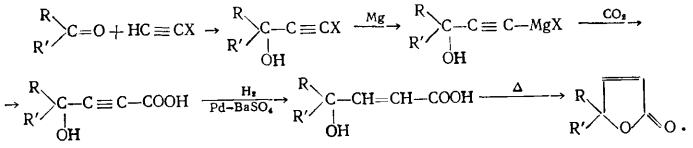
†2(5*H*)-furanones (Ed. of Translation).

$\Delta^{\alpha\beta}$-Butenolides are obtained by the reaction of β-benzoyl-α-phenylpropionic acid and its derivatives with acetyl chloride[18], acetic anhydride[19], and sulphuric acid[20]. This reaction is acoompanied by the formation of $\beta\gamma$-isomers[21,22] and bislactones[23-26]. The reaction of esters of these acids with aromatic aldehydes in the presence of bases leads to γ-hydroxy-$\Delta^{\alpha\beta}$-butenolides[27-29].

When benzylidinepyruvic acid reacts with aromatic amines, the products are γ-aryl-α-arylamino-$\Delta^{\alpha\beta}$-butenolides[30-33] whose condensation with o-nitrobenzaldehyde leads to α-hydroxy-γ-(o-nitrophenyl)-$\Delta^{\alpha\beta}$-butenolide[34]. The reaction of acrolein with cyanoacetic acid yields α-cyano-$\Delta^{\alpha\beta}$-butenolides[35].

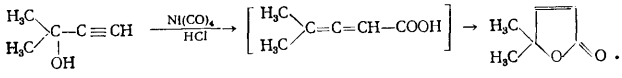
2. The Synthesis of $\Delta^{\alpha\beta}$-Butenolides from $\alpha\beta$-Unsaturated Carboxylic Acids and Their Derivatives

An important method for the synthesis of $\Delta^{\alpha\beta}$-butenolides is the intramolecular cyclisation of $\alpha\beta$-unsaturated carboxylic acids and their derivatives. When ethyl crotonate is heated with selenium dioxide, a $\Delta^{\alpha\beta}$-butenolide is obtained[36]. Acetylenecarboxylic acids are reduced to olefinic acids, which likewise can cyclise to the corresponding $\Delta^{\alpha\beta}$-butenolides on heating[37,38]:



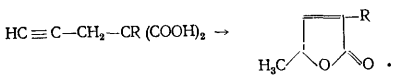
The intramolecular cyclisation of $\alpha\beta$-unsaturated carboxylic acids and their derivatives apparently proceeds via a mechanism which has been generally adopted for the formation of esters from acids and alcohols.

A variation of this reaction is the conversion of an acetylenic alcohol into $\Delta^{\alpha\beta}$-butenolide on heating with nickel carbonyl in a butanol–hydrochloric acid mixture[39]. It is suggested that the reaction proceeds via an allenecarboxylic acid:

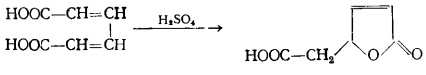


$\Delta^{\alpha\beta}$-Butenolide is also obtained when acetylene is heated with acetone and acetic anhydride in an autoclave at 100°C and under a pressure of 250 atm in the presence of dicobalt octacarbonyl[40,41].

In the presence of acid or alkaline catalysts, acetylenecarboxylic and acetylenedicarboxylic acids cyclise to $\Delta^{\alpha\beta}$-butenolides. The corresponding $\Delta^{\alpha\beta}$-butenolide and dilactones have been obtained by this reaction from various alkyl- and aryl-substituted malonic acids containing the propargyl or dipropargyl group[42-44]:

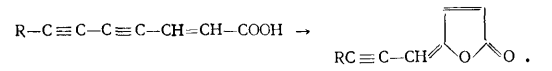


Carboxylic acids with two double bonds can be converted into lactones by treatment with sulphuric acid. Thus, the lactonisation of muconic acid results in the formation of γ-carboxymethyl-$\Delta^{\alpha\beta}$-butenolide[45,46]:



When monobasic or dibasic enynoic acids‡ are heated, they cyclise with formation of $\Delta^{\alpha\beta}$-butenolides of the type of protoanemonine derivatives[47-49].

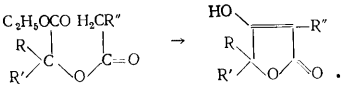
The cyclisation of endiynoic acids leads to $\Delta^{\alpha\beta}$-butenolides with an acetylenic group[54]:



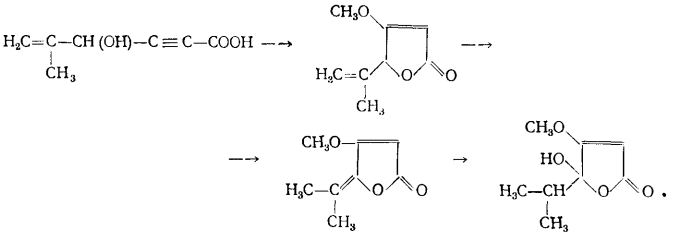
3. The Preparation of $\Delta^{\alpha\beta}$-Butenolides from Hydroxy- and Halogeno-Acids and Their Derivatives

The cyclodehydration of saturated and unsaturated hydroxyacids and their derivatives is widely used to synthesise $\Delta^{\alpha\beta}$-butenolides. Natural products such as vitamin C, dihydropenicilloic acid, etc. have been synthesised by this method.

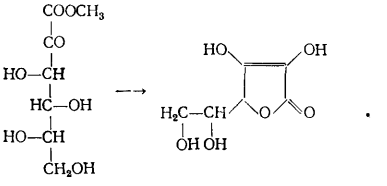
When α-hydroxyacid diesters are heated in the presence of metallic sodium, tetronic acids are formed[55]:



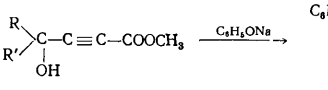
On heating, 3,4-dihydroxybutyric acid with phosphorus pentoxide, $\Delta^{\alpha\beta}$-butenolide is formed and can be obtained also from 3,4-dichlorobutyric acid when the latter is heated with potassium carbonate or a methanol solution of sodium hydroxide[56]. γ-Isopropenyl-β-methoxy-$\Delta^{\alpha\beta}$-butenolide has been synthesised by intramolecular cyclisation of 4-hydroxy-5-methylhex-5-en-2-ynoic acid in the presence of BF_3.HgO in methanol. The butenolide is converted by treatment with an aqueous alcoholic solution of alkali into γ-hydroxy-γ-isopropyl-β-methoxy-$\Delta^{\alpha\beta}$-butenolide (dihydropenicilloic acid)[57,58]:



When methyl 2-oxogulonate is heated in methanol solution in the presence of sodium carbonate in an atmosphere of nitrogen, the product is vitamin C (L-ascorbic acid)[59]:

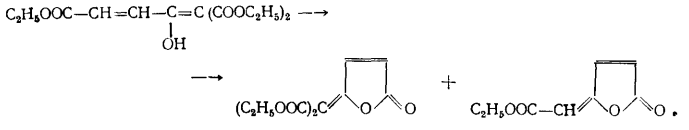


$\gamma\gamma$-Dialkyl-β-phenoxy-$\Delta^{\alpha\beta}$-butenolides have been obtained by the reaction of sodium phenoxide with the methyl esters of γ-hydroxyacetylenic acids[60]:

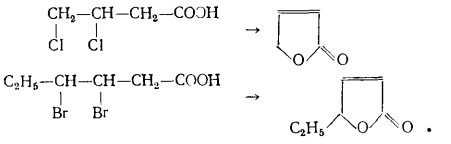


‡It is of interest that these acids cyclise to 2-pyrones under the influence of strongly basic catalysts[47,48,50-53].

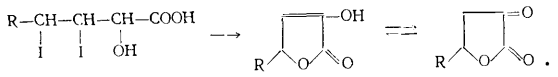
Muconic acid derivatives have been used[61] as the starting materials for the synthesis of unsaturated $\Delta^{\alpha\beta}$-butenolides; thus pyrolysis of diethyl β-hydroxy-α-ethoxycarbonylmuconate leads to a mixture of diunsaturated lactones—derivatives of the type of protoanemonine:



Halogenocarboxylic acids and their derivatives have also been used as the starting materials for the synthesis of unsaturated $\Delta^{\alpha\beta}$-butenolides. The corresponding $\Delta^{\alpha\beta}$-butenolides are obtained by the dehydrohalogenation of $\beta\gamma$-dihalogenobutyric[62,63] and $\beta\gamma$-dibromocaproic[64] acids in the presence of sodium carbonate, sodium bicarbonate, or triethylamine:

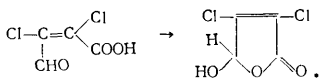


γ-Alkyl-α-hydroxy-$\Delta^{\alpha\beta}$-butenolides, which are in equilibrium with the keto-forms, have been synthesised by the elimination of water from α-hydroxy-$\beta\gamma$-diiodocarboxylic acids[65]:



β-Formyl-$\alpha\beta$-dihalogenoacrylic acids condensed with phenol, anisole, guaiacol, thymol, halogenobenzene, 1,2,3-trimethoxybenzene, and *o*-dimethoxybenzene in the presence of inorganic or Lewis acids to form γ-substituted $\Delta^{\alpha\beta}$-butenolides[66-69].

Halogenomuconate esters exist in the cyclic lactone form[70]:

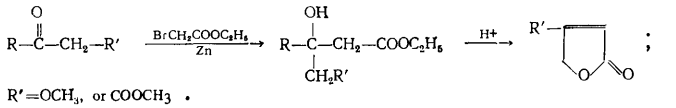


When chloromuconic acid condenses with acetophenone, nitromethane, or nitroethane in the presence of sodium hydroxide, γ-substituted $\alpha\beta$-dichloro-$\Delta^{\alpha\beta}$-butenolides are obtained[71,72]; the condensation of the acid with benzene and chlorobenzene yields respectively $\alpha\beta$-dichloro-γ-phenyl-$\Delta^{\alpha\beta}$-butenolide and $\alpha\beta$-dichloro-γ-(*p*-chlorophenyl)-$\Delta^{\alpha\beta}$-butenolide[24,73] and the condensation with aromatic compounds (phenol and anisole) in the presence of polyphosphoric acid gives rise to $\alpha\beta$-dichloro-$\Delta^{\alpha\beta}$-butenolides[68,74].

Bromomuconic acid reacts with acetophenone to form $\alpha\beta$-dibromo-γ-phenacyl-$\Delta^{\alpha\beta}$-butenolide[75].

4. The Synthesis of $\Delta^{\alpha\beta}$-Butenolides by the Reformatsky Reaction

An important method for the synthesis of $\Delta^{\alpha\beta}$-butenolides and steroid lactones is the Reformatsky reaction. The starting materials in this case are α-methoxy- or acetoxy-ketones. This method of synthesis of $\Delta^{\alpha\beta}$-butenolides has been used by many investigators[76-99]:



The acetoxyester is converted into the $\Delta^{\alpha\beta}$-butenolide by heating it in the presence of alkali metal hydrogen sulphates, anhydrous oxalic acid, or potassium phosphate[100]. The intramolecular Reformatsky reaction, i.e. the interaction of the above compounds with zinc or magnesium in inert solvents, constitutes a modification of this process[101].

5. The Synthesis of $\Delta^{\alpha\beta}$-Butenolides from the Corresponding $\Delta\beta\gamma$-Isomers

Under the influence of bases such as triethlyamine, piperidine, and benzylamine, $\Delta\beta\gamma$-butenolides are converted into the corresponding $\Delta^{\alpha\beta}$-isomers[8,102,103]. Acetic anhydride is sometimes used as the catalyst for this purpose[104,105].

6. The Synthesis of $\Delta^{\alpha\beta}$-Butenolides from Substituted γ-Butyrolactones

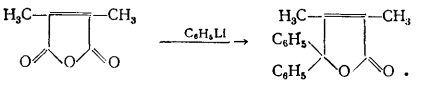
When saturated γ-lactones containing substituents (OH, $OOCCH_3$, SH, NH_2) in the α- or γ-positions are treated with acids or salts, the HX molecule is split off with formation of a mixture of $\Delta^{\alpha\beta}$- and $\Delta^{\beta\gamma}$-isomers. Treatment of the mixture with a base leads to the pure $\Delta^{\alpha\beta}$-isomer[106,107].

For example, α-chloro-β-cyclohexylbutyrolactone is converted into β-cyclohexyl-$\Delta^{\alpha\beta}$-butenolide under the influence of potassium acetate[108,109]. β-Aroyl-β-bromoacrylic acids, which exist in the cyclic form, have been converted into the corresponding $\Delta^{\alpha\beta}$-butenolides[110-112]. A solution of γ-benzoyl-β-phenylacrylic acid contains approximately 70% of γ-hydroxy-$\alpha\beta$-diphenyl-$\Delta^{\alpha\beta}$-butenolide[109].

Pyrolysis of saturated γ-lactones containing substituents (H, C_7H_{15} or C_2H_5, OAc) in the γ-position, in the presence of sulphuric acid at 200–330°C, gives rise to γ-alkyl-$\Delta^{\alpha\beta}$-butenolides[114]. γ-Substituted $\Delta^{\alpha\beta}$-butenolides are obtained by the oxidative decarboxylation of γ-substituted paraconic acid in the presence of $Na_2S_2O_8$, $AgNO_3$, and $CuSO_4$.[115]

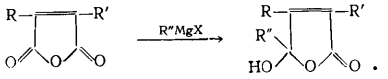
7. The Synthesis of $\Delta^{\alpha\beta}$-Butenolides from Substituted Maleic Acid Anhydrides

The next most important method of synthesis of $\Delta^{\alpha\beta}$-butenolides involves the interaction of a substituted maleic anhydride with organometallic compounds. Thus the reaction of dimethylmaleic anhydride with phenyllithium yields $\alpha\beta$-dimethyl-$\gamma\gamma$-diphenyl-$\Delta^{\alpha\beta}$-butenolide[116]:



γ-Alkyl-γ-hydroxy-$\Delta^{\alpha\beta}$-butenolides have been obtained by the reaction of mono- and di-alkylmaleic anhydrides with alkylmagnesium or arylalkylmagnesium halides[117].

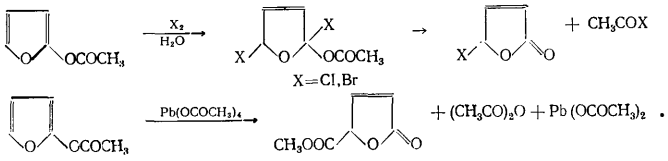
Dehydration of these butenolides leads to α-alkylidene-$\Delta^{\alpha\beta}$-butenolides [117]:



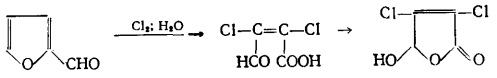
$\gamma\gamma$-Disubstituted $\alpha\beta$-dimethyl-$\Delta^{\alpha\beta}$-butenolides are obtained by the Friedel-Crafts reaction from dimethylmaleic anhydride and biphenyl in carbon disulphide [118].

8. The Synthesis of $\Delta^{\alpha\beta}$-Butenolides from Furan and Furancarboxylic Acid Derivatives

The reaction of 2-acetoxyfuran with halogens (chlorine or bromine) in the presence of water or lead tetraacetate results in the synthesis of γ-halogeno- or γ-acetoxy-$\Delta^{\alpha\beta}$-butenolides [119]:



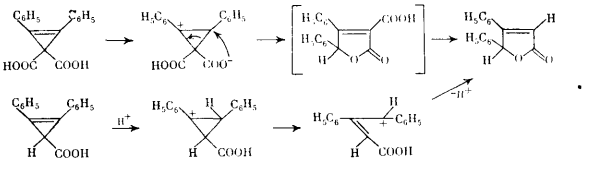
When bromine is allowed to react with pyromucic acid in the presence of water, a complex process takes place—decarboxylation, addition of bromine, and oxidation with formation of $\alpha\beta$-dibromo-γ-hydroxy-$\Delta^{\alpha\beta}$-butenolide [120]. $\alpha\beta$-Dichloro-γ-hydroxy-$\Delta^{\alpha\beta}$-butenolide is obtained when chlorine and furfural are added simultaneously to a concentrated solution of hydrochloric acid at 70°C [121]:



Acid hydrolysis of methyl 3,4-dihalogeno-2,5-dimethoxytetrahydrofurancarboxylates leads to $\alpha\beta$-dihalogeno-$\Delta^{\alpha\beta}$-butenolides [122].

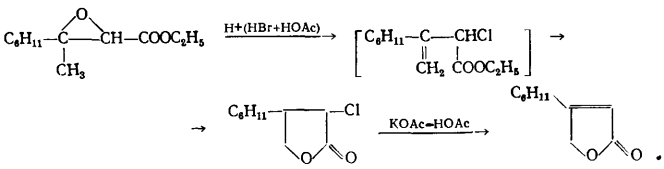
9. The Synthesis of $\Delta^{\alpha\beta}$-Butenolides from Cyclopropane Derivatives

The reaction of diphenylacetylene with diazomalonic ester in the presence of copper leads to 1,2-diphenylcyclopropane-3,3-dicarboxylic acid, the thermal decomposition of which results in the formation of $\beta\gamma$-diphenyl-$\Delta^{\alpha\beta}$-butenolide [123]. This butenolide is also obtained from acetic acid derivatives and from 1,2-diphenylcyclopropane-3-carboxylic acid in the presence of acid catalysts [124-126]:

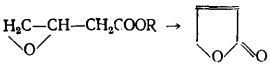


10. The Synthesis of $\Delta^{\alpha\beta}$-Butenolides from Epoxy-Compounds

$\Delta^{\alpha\beta}$-Butenolides are also obtained from epoxy-compounds. Thus ethyl 3-cyclohexyl-2,3-epoxybutyrate, which is readily formed by the Darzens reaction, is converted in the presence of catalysts into β-cyclohexyl-$\Delta^{\alpha\beta}$-butenolide [108,109]:



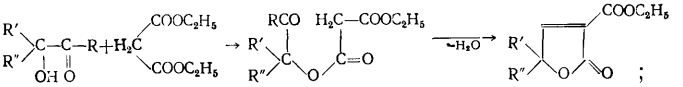
On treatment with sulphuric acid, esters of 3,4-epoxybutyric acid are converted into $\Delta^{\alpha\beta}$-butenolide [127]:



11. The Synthesis of $\Delta^{\alpha\beta}$-Butenolides from Hydroxyketo-Compounds

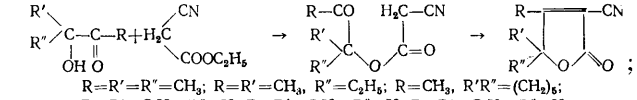
An important disadvantage of the above methods is the difficulty of introducing various functional groups into the unsaturated lactone ring. For this reason, the condensation of hydroxyketones with esters containing active methylene groups§ may be regarded as the most general method of synthesis of $\Delta^{\alpha\beta}$-butenolides with functional groups. The esters with active methylene groups employed are the acetoacetic, benzoylacetic, malonic, cyanoacetic, phenylacetic, and similar compounds, for example diketen.

Thus acyloins and tertiary α-ketoalcohols interact with ethyl malonate in the presence of alkaline catalysts to form substituted α-ethoxycarbonyl-$\Delta^{\alpha\beta}$-butenolides [128-133]. Sodium ethoxide is an effective catalyst for this reaction [132,133]:



R=R′=R″=CH$_3$; R=R′=CH$_3$, R″=C$_2$H$_5$; R=CH$_3$, R′R″=(CH$_2$)$_5$; R=R′=C$_2$H$_5$, R″=H; R=R′=C$_3$H$_7$, R″=H; R=R′=C$_4$H$_9$, R″=H; R=R′=C$_5$H$_{11}$, R″=H .

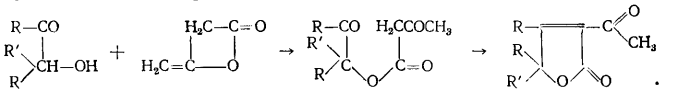
As is to be expected, cyanoacetic ester condenses with α-ketoalcohols in the presence of a basic catalyst more readily than malonic acid, the product being substituted α-cyano-$\Delta^{\alpha\beta}$-butenolides [133,134]:



R=R′=R″=CH$_3$; R=R′=CH$_3$, R″=C$_2$H$_5$; R=CH$_3$, R′R″=(CH$_2$)$_5$; R=R′=C$_2$H$_5$, R″=H; R=R′=C$_3$H$_7$, R″=H; R=R′=C$_4$H$_9$, R″=H; R=R′=C$_5$H$_{11}$, R″=H.

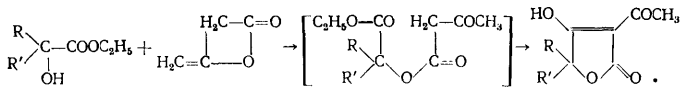
Under analogous conditions, benzoin reacts with cyanoacetic ester to form α-cyano-βγ-diphenyl-$\Delta^{\alpha\beta}$-butenolide [135].

The esters of acyloins and acetoacetic acid can undergo intramolecular condensation with formation of $\Delta^{\alpha\beta}$-butenolides. For example, acyloins and tertiary α-ketoalcohols react with diketen in the presence of pyridine or triethylamine to form acetoacetic acid esters, which cyclise on heating to substituted $\Delta^{\alpha\beta}$-butenolides [136-138]:

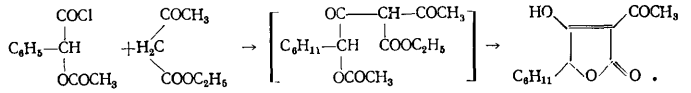


§Among the advantages of this method, one may note the ready availability of the initial compounds and the simple technology of the process.

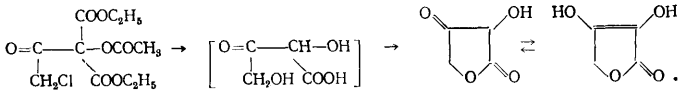
Under analogous conditions α-hydroxyacid esters also react with diketen to form the corresponding Δαβ-butenolides—acetyltetronic acids [136,139]



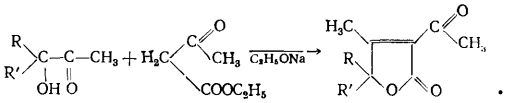
In order to synthesise tetronic acid derivatives, the chloride of acetoxy-mandelic acid was allowed to react with acetoacetic ester [140], which resulted in the formation of α-acetyl-β-hydroxy-γ-phenyl-Δαβ-butenolide:



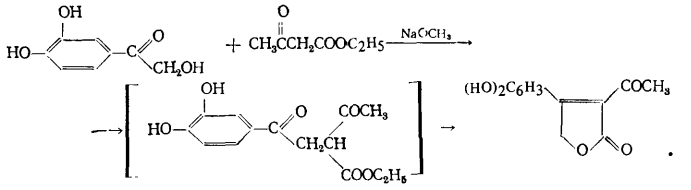
A number of acylated malonic and cyanoacetic acids have also been used for the same purpose [140]. Thus α-hydroxytetronic acid has been obtained from diethyl acetoxychloroacetylmalonate in the presence of base [141]:



The condensation of tertiary α-ketoalcohols with acetoacetic esters in the presence of sodium ethoxide proceeds with formation of the corresponding α-acetyl-Δαβ-butenolides [134]:

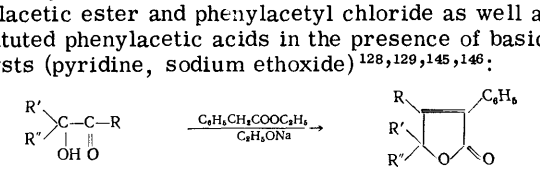


ω-Hydroxyacetophenones containing hydroxy-groups in the benzene ring interact with acetoacetic ester in methanol solution to form Δαβ-butenolides [142-144]:



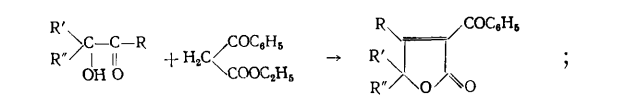
2-Methyl-3,3-di-(*p*-tolyl)propionic acid, which gives rise to a mixture of Δαβ-Δβγ-isomers on heating with acetic anhydride, was obtained similarly from acetophenone and β-benzoacrylic [β-benzoylacrylic?] acid [108]. [This paragraph is completely erroneous. 2-Methyl-3,3-di-(*p*-tolyl)-propionic acid is not mentioned in Ref. 108 nor in Refs. 142 to 144 (Ed. of Translation)].

Substituted α-phenyl-Δαβ-butenolides have been synthesised by the condensation of α-ketoalcohols with phenylacetic ester and phenylacetyl chloride as well as substituted phenylacetic acids in the presence of basic catalysts (pyridine, sodium ethoxide) [128,129,145,146]:



R=R′=R″=CH_3; R=R′=CH_3, R″=C_2H_5; R=CH_3, R′R″=$(CH_2)_5$; R=R′=C_2H_5, C_3H_7 or C_4H_9, R″=H.

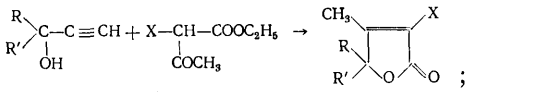
Secondary and tertiary α-ketoalcohols are converted into the corresponding α-benzoyl-Δαβ-butenolides on condensation with benzoylacetic ester in the presence of sodium ethoxide [147,148]:



R=R′=R″=CH_3; R=R′=CH_3, R″=C_2H_5; R=CH_3R′R″=$(CH_2)_5$; R=R′=C_2H_5, C_3H_7,C_4H_9, R″=H.

The ability of the above esters to form lactones in condensation reactions with α-ketoalcohols diminishes in the sequence cyanoacetic > acetoacetic > malonic > benzoylacetic > phenylacetic. A probable reaction mechanism has been proposed [132,133,138].

Acetylenic carbinols have also been used as starting materials for the synthesis of Δαβ-butenolides. Thus Lacey [138] obtained α-acetyl- or α-ethoxy-carbonyl-Δαβ-butenolides by the reaction of ethynylmethanols with acetylacetoacetic or acetylmalonic esters at 135-200°C:



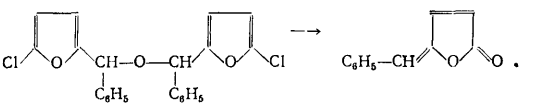
X=$COCH_3$ $COOC_2H_5$.

12. Oxidation with Peracids

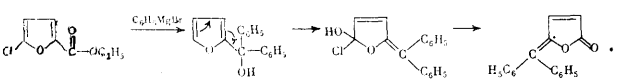
When 2,5-dimethylphenol is oxidised with peracids, the product is αα′-dimethyl-*cis*,*cis*-muconic acid, which is converted into γ-ethoxycarbonyl-α-methyl-Δαβ-butenolide on heating in ethanol [149].

13. The Synthesis of γ-Arylidene- and γ-Alkylidene-Δαβ-Butenolides

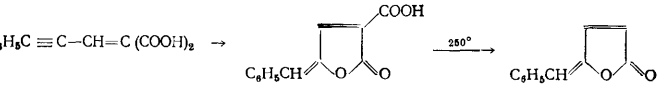
When bis-(5-chlorofuryl-2-methylphenyl) ether reacts with concentrated sulphuric acid, γ-benzylidene-Δαβ-butenolide is formed [150]:



γ-Diphenylmethylene-Δαβ-butenolide has been synthesised from ethyl 5-chlorofuran-2-carboxylate on treatment with phenylmagnesium bromide [150]:



When malonic acid reacts with phenylpropargylaldehyde, the product is phenylpropargylidenemalonic acid, which is converted into γ-benzylidene-α-carboxy-Δαβ-butenolide on heating to 190°C. [48] The decarboxylation of this product at 250°C leads to γ-benzylidene-Δαβ-butenolide [48,151]:

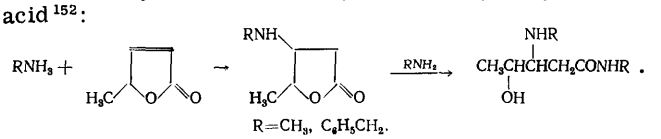


When mono- or di-alkylmaleic anhydrides are treated with a Grignard reagent at low temperatures, di- or tri-substituted γ-hydroxy-Δαβ-butenolides are obtained [117]. Their dehydration with a mixture of acetic anhydride, acetic acid and sulphuric acid leads to γ-alkylidene or γ-arylidene-Δαβ-butenolides [117].

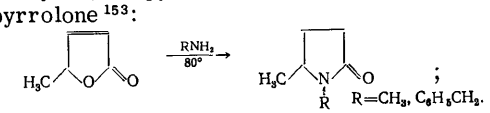
III. CHEMICAL PROPERTIES OF $\Delta^{\alpha\beta}$-BUTENOLIDES

$\Delta^{\alpha\beta}$-Butenolides are very reactive. Owing to the presence of reactive centres such as the double bond and the lactone ring, they can react with nucleophiles and electrophiles and can undergo other reactions involving both the retention and the opening of the lactone ring.

$\Delta^{\alpha\beta}$-Butenolides react with ammonia and amines in different ways. Jones and Young [152] showed that, when angelica lactone reacts with aqueous methylamine and benzylamine solutions at room temperature, the amines add to the unsaturated carbon–carbon bond in the lactone ring [152]. Since the distribution of electron density in the lactone ring is such that there is a deficiency of electron density at the second and fifth carbon atoms in the ring, presumably nucleophiles attack one of these carbon atoms with subsequent dissociation of the $C_{(1)}-C_{(2)}$ or $C_{(1)}-C_{(5)}$ bond and formation of the corresponding derivative. The product obtained, which is a derivative of butyrolactone, therefore reacts with a second amine molecule to form the methylamide of γ-hydroxy-β-methylaminovaleric acid and the benzylamide of β-benzylamino-γ-hydroxyvaleric acid [152]:

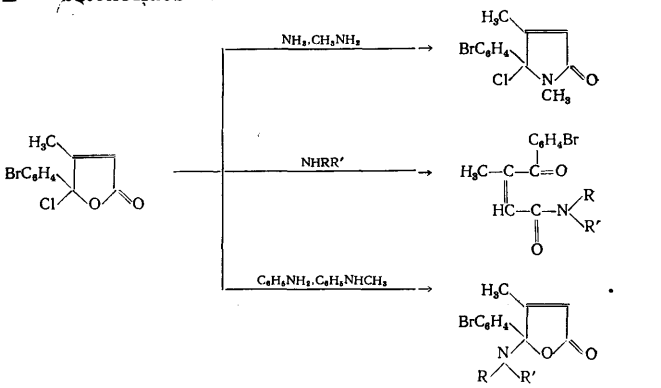


However, when angelica lactone is heated with an equimolar amount of methylamine or benzylamine to 80°C, 1,5-dimethyl-2(5*H*)-pyrrolone and 1-benzyl-5-methyl-2(5*H*)-pyrrolone [153]:

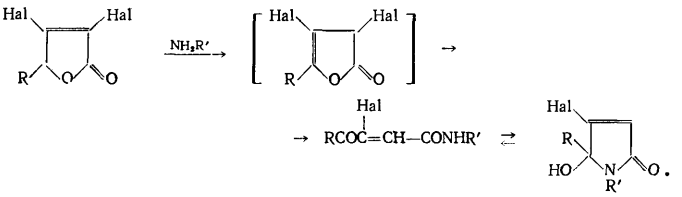


The reactions of halogenobutenolides with ammonia or amines can proceed in the following ways: opening of the butenolide ring with formation of the corresponding amide of a hydroxy- or an amino-acid [154–157], nucleophilic substitution of the halogen by an amino-residue [30,154–157], and addition of an amine to the C=C bond of the $\Delta^{\alpha\beta}$-butenolide ring [152]. The particular pathway followed in the reaction with a given nucleophile is apparently determined mainly by the thermodynamic stability of the addition products formed [158].

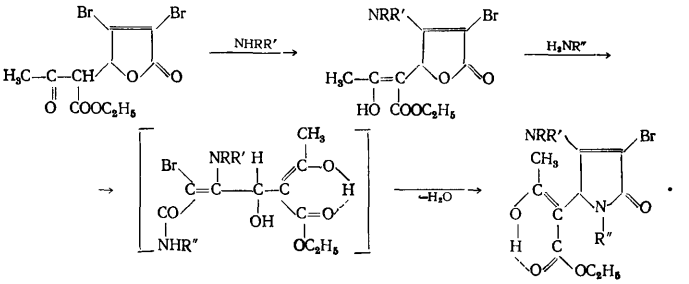
For example, when γ-(bromophenyl)-γ-chloro-β-methyl-$\Delta^{\alpha\beta}$-butenolide reacts with ammonia at room temperature in benzene, the product is a γ-hydroxylactam, the reaction with dimethylamine yields the alkylamide of *cis*-β-(*p*-bromobenzoyl)-β-methylacrylic acid, and the reaction with aniline or methylaniline results in the formation of γ-(*N*-arylamino)-γ-(bromophenyl)-β-methyl-$\Delta^{\alpha\beta}$-butenolides [30]:



It has been shown [156,157] that, when $\alpha\beta$-dihalogeno-$\Delta^{\alpha\beta}$-butenolides are treated with primary amines in methanol at temperatures between −5° and −10°C, the butenolide ring opens with formation of an amide, which readily cyclises under the reaction conditions and is in equilibrium with the corresponding lactam:

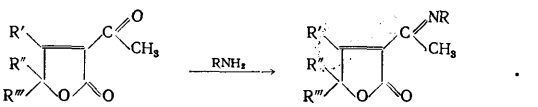


When $\alpha\beta$-dibromo-γ-(α'-ethoxycarbonylacetonyl)-$\Delta^{\alpha\beta}$-butenolide reacts with a twofold excess of a primary or secondary amine in methanol, the nucleophilic substitution of the halogen by the amino-residue takes place without involving the lactone ring; the products are β-amino-α-bromo-$\Delta^{\alpha\beta}$-butenolides, which are converted into the corresponding $\Delta^{\alpha\beta}$-crotonolactams at room temperature in dioxan [159]:

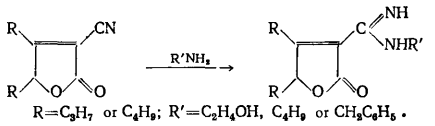


Bromine is substituted in the β-position, which can be explained by the fact that the electron density is a minimum at the corresponding carbon atom [160].

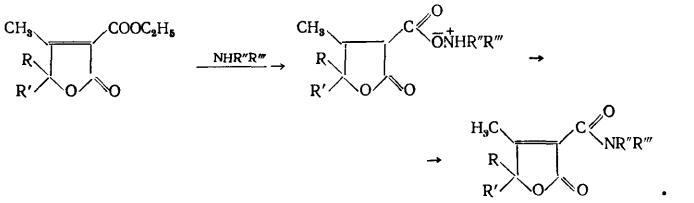
When substituted α-acetyl-$\Delta^{\alpha\beta}$-butenolides react with primary amines, the nucleophilic attack by the amine is directed exclusively to the acetylcarbonyl group with formation of the corresponding amino-derivatives of α-acetyl-$\Delta^{\alpha\beta}$-butenolides [161]:



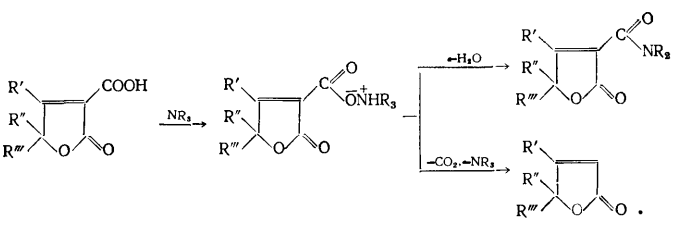
Primary amines add to the cyano-group of substituted α-cyano-$\Delta^{\alpha\beta}$-butenolides with formation of the aminidines of the corresponding lactones [162]:



The reaction of substituted α-ethoxycarbonyl-$\Delta^{\alpha\beta}$-butenolides with primary and secondary amines proceeds via the nucleophilic attack by the amine exclusively on the ester group, with formation of the amides of salts of substituted γ-lactonoacids, i.e. the reactions proceed without the opening of the lactone ring [163–165]:

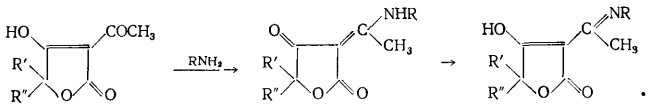


$\beta\gamma\gamma$-Trialkyl-α-carboxy-$\Delta^{\alpha\beta}$-butenolides readily react with aqueous ammonia and aniline solutions and with primary and secondary amines to form the ammonium salts of α-carboxy-$\Delta^{\alpha\beta}$-butenolides [164]:

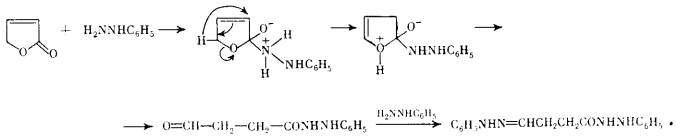


Depending on the nature of the amine, the salts decompose in two ways with formation of the amidolactones of α-carboxy-$\Delta^{\alpha\beta}$-butenolides and $\beta\gamma\gamma$-trialkyl-$\Delta^{\alpha\beta}$-butenolides. In both cases the unsaturated lactone ring remains unchanged [164].

When α-acetyltetronic acids are heated with ammonia and primary amines, imino-derivatives of tetronic acid are formed [139]:

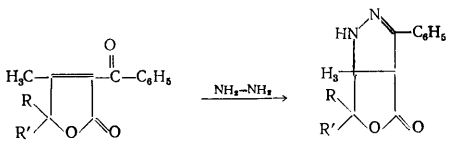


The reaction of $\Delta^{\alpha\beta}$-butenolides with phenylhydrazine entails the dissociation of the $C_{(1)}-C_{(2)}$ bond of the lactone ring with formation of the phenylhydrazide-phenylhydrazone of formylsuccinic acid [166]; the authors represent the reaction by the following scheme:



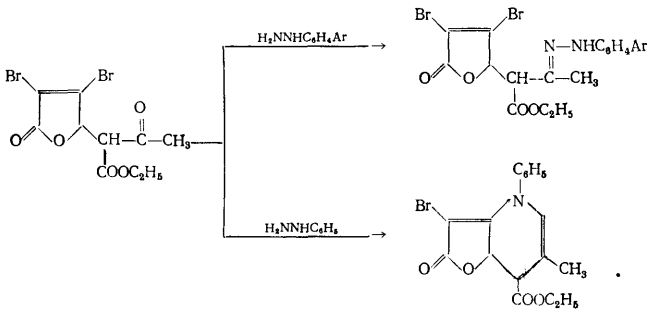
The reaction of α- and β-acetyl-$\Delta^{\alpha\beta}$-butenolides with hydrazine, phenylhydrazine, and hydroxylamine at room temperature involves the oxo-group without the opening of the lactone ring and without addition to the double bond [161,167].

The reaction of hydrazine with substituted α-benzoyl-$\Delta^{\alpha\beta}$-butenolides yields pyrazolines containing the γ-lactone ring [168]:



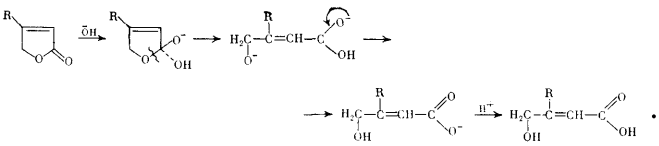
Similar pyrazolines were obtained also by the reaction of $\Delta^{\alpha\beta}$-butenolides with aliphatic diazo-compounds [169].

Kalnina and Gudriniece [159] showed that the reaction of $\alpha\beta$-dibromo-γ-(α'-ethoxycarbonylacetonyl)-$\Delta^{\alpha\beta}$-butenolide with p-nitro- and 2,4-dinitro-phenyl-hydrazines at room temperature yields the corresponding arylhydrazones, while the reaction of $\alpha\beta$-dibromo-$\Delta^{\alpha\beta}$-butenolide with phenylhydrazine involves also the elimination of hydrogen bromide and the closure of the tetrahydropyridazine ring [159]:

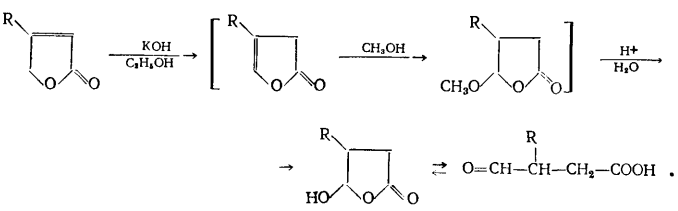


Thus the study of the reactions with ammonia and nitrogen-containing bases showed that, in contrast to the saturated analogues, the lactone ring in unsaturated substituted butenolides is unreactive towards nucleophiles. Comparative studies of the reactivities of the functional groups and the double bond clearly demonstrated the much weaker electrophilic properties of the double bond in these reactions.

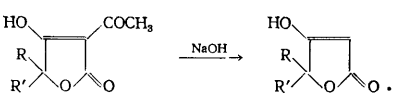
$\Delta^{\alpha\beta}$-Butenolides are hydrolysed with and without the opening of the lactone ring. The ease of ring opening in hydrolysis depends on the nature and positions of the substituents. Thus when β-substituted $\Delta^{\alpha\beta}$-butenolides were acted upon by alkali, two different reactions were noted [86]. In an aqueous medium, the lactone hydrolyses, forming the salt of the corresponding acid [86]:



In alcoholic solution, the double bond migrates irreversibly to the $\beta\gamma$-position and the resulting vinyl ether combines with the elements of the alcohol to form an acetal. After acidification, the acetal hydrolyses to the hydroxylactone, which exists in equilibrium with the non-cyclic formyl-substituted acid [86]:

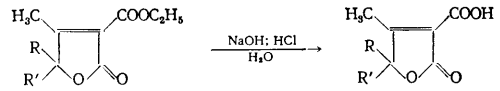


On treatment with aqueous solutions of alkali, the unsaturated lactone ring in α-acetyl-γ-methyl- and α-acetyl-$\gamma\gamma$-diphenyltetronic acids remain unchanged, the products being γ-alkyltetronic acids [139]:

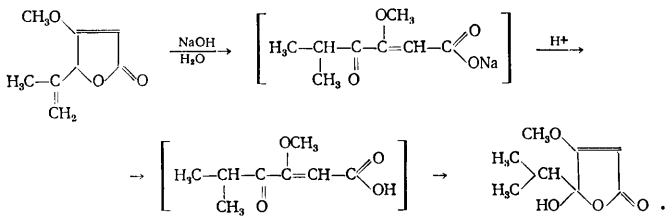


Alkaline and acid hydrolysis of substituted α-ethoxycarbonyl-$\Delta^{\alpha\beta}$-butenolides involves only the ethoxycarbonyl

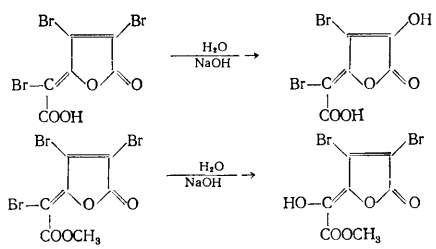
group with retention of the lactone ring and the formation of α-carboxy-$\Delta^{\alpha\beta}$-butenolides [163,164]:



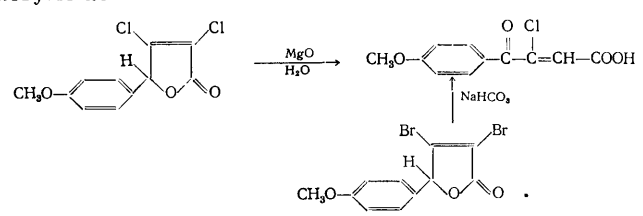
Killian et al.[170] showed that, when penicilloic acid reacts with a cold dilute solution of sodium hydroxide, dihydropenicilloic acid is formed. It is suggested that treatment with alkali involves a shift of the double bond with subsequent opening and reclosure of the lactone ring:



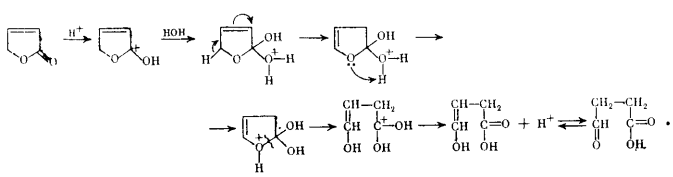
The alkaline hydrolysis of halogeno-$\Delta^{\alpha\beta}$-butenolides involves only the halogen with retention of the lactone ring. Thus the alkaline hydrolysis of the γ-lactone and the methyl ester of the γ-lactone of $\alpha\beta\delta$-tribromomuconic acid yields respectively the γ-lactone of $\beta\gamma$-dibromo-α-hydroxymuconic acid[171] and the γ-lactone of the methyl ester of $\alpha\beta$-dibromo-δ-hydroxymuconic acids[172]:



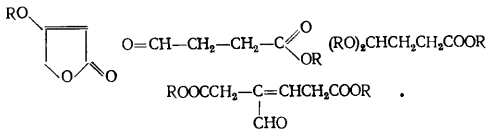
Hydrolysis of halogeno-$\Delta^{\alpha\beta}$-butenolides also proceeds on treatment with magnesium oxide in aqueous dioxan or in sodium bicarbonate solution with formation of acrylic acid derivatives[173]:



Acid hydrolysis of γ-lactones, which proceeds with opening of the lactone ring, has been described only for an unsaturated $\Delta^{\alpha\beta}$-butenolide[166]. The opening of the $\Delta^{\alpha\beta}$-butenolide ring in an acid medium is accompanied by the appearance of the formyl group and leads to the formation of 4-hydroxybut-3-enoic acid, which is converted into the tautomeric formylsuccinic acid[166]:

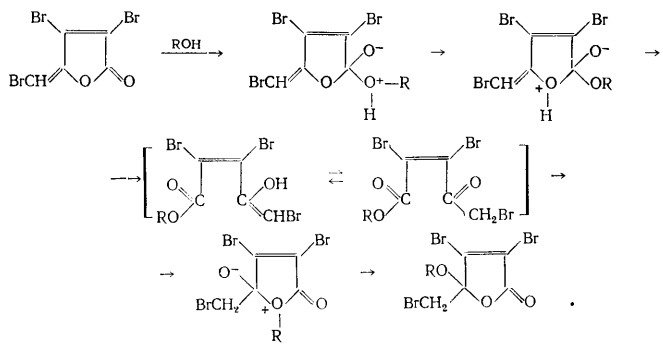


Alcoholysis of $\Delta^{\alpha\beta}$-butenolides takes place in the presence of acid catalysts (in the absence of catalysts, the reaction proceeds only slowly and requires prolonged heating) and leads to the formation of hydroxyacids. Thus heating of a $\Delta^{\alpha\beta}$-butenolide with alcohols leads to a mixture of products[12,166,174-176], which were isolated by fractional distillation and identified by the formation of various derivatives and by infrared and Raman spectroscopy:



$\Delta^{\alpha\beta}$-Butenolides react with alcohols in the presence of hydrogen chloride[43] or thionyl chloride[174] with formation of hydroxyacid esters.

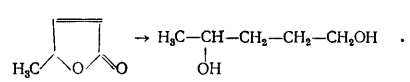
The reaction of $\alpha\beta$-dibromo-γ-bromomethylene-$\Delta^{\alpha\beta}$-butenolide with alcohols on boiling leads to the formation of γ-alkoxy-$\alpha\beta$-dibromo-γ-bromomethyl-$\Delta^{\alpha\beta}$-butenolides[177]. The initial products are apparently esters, whose conversion into a cyclic form involves the stabilisation of oxonium derivatives of $\Delta^{\alpha\beta}$-butenolides:



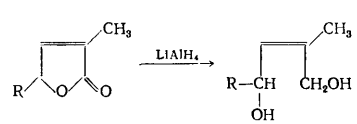
Systematic study of the catalytic hydrogenation of $\Delta^{\alpha\beta}$-butenolides showed that they readily react with hydrogen at the double bond, being converted into the corresponding butyrolactone derivatives[139,162,165,178,179]. Palladium black, Raney nickel, and palladium calcium on carbonate are used as catalysts.

The catalytic hydrogenation of α-ethoxycarbonyl, α-carboxy-, α-carbamoyl, α-acetyl, and α-cyano-$\Delta^{\alpha\beta}$-butenolides over $Pd/CaCO_3$ proceeds selectively, involving the unsaturated bond of the lactone ring, and leads to the synthesis of the corresponding butyrolactone derivatives[139,162,165].

The effect of complex metal hydrides on $\Delta^{\alpha\beta}$-butenolides has been investigated[180-182]. $\Delta^{\alpha\beta}$-Butenolides are reduced by lithium tetrahydroaluminate to the corresponding diols. Thus pentane-1,4-diol is obtained when β-angelica lactone is treated with lithium tetrahydroaluminate[183]:



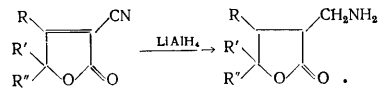
The reduction of α-methyl-γ-phenyl-$\Delta^{\alpha\beta}$-butenolide and α-methyl-γ-(2-naphthyl)-$\Delta^{\alpha\beta}$-butenolide leads to the corresponding diols[181]:



The opening of the lactone ring is observed also when $\Delta^{\alpha\beta}$-butenolides react with dimethyl- and diethyl-aluminium chlorides[184]. Ketoalcohols and the corresponding unsaturated and saturated diols are obtained for different

proportions of the lactone and lithium tetrahydroaluminate taken for the reaction[181-183].

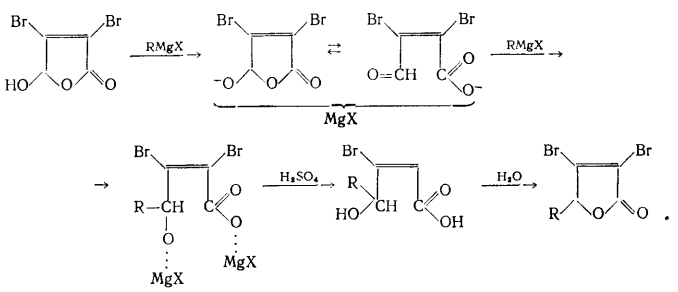
The reduction of substituted α-cyano-Δ$^{\alpha\beta}$-butenolides with lithium tetrahydroaluminate involves the cyano-group with simultaneous reduction of the unsaturated bond in the lactone and leads to α-aminomethylbutyrolactones[182]:



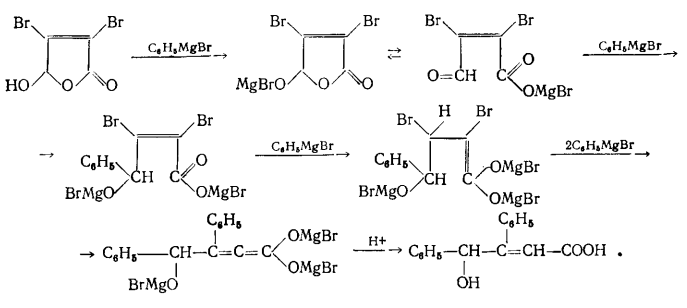
α-Hydroxymethyl-, α-(1-hydroxyethyl)-, and α-(1-hydroxybenzyl)-Δ$^{\alpha\beta}$-butenolides have been obtained under analogous conditions from α-ethoxycarbonyl, α-acetyl-, and α-benzoyl-Δ$^{\alpha\beta}$-butenolides[182].

Since Δ$^{\alpha\beta}$-butenolides can be regarded as dihydrofuranones, one may expect that they can be readily converted into furan derivatives. Thus α-acetyl-Δ$^{\alpha\beta}$-butenolides undergo a very interesting rearrangement. When α-acetyl-Δ$^{\alpha\beta}$-butenolides [i.e. 3-acetyl-2(5*H*)-furanones] are heated with a mixture of acetic and hydrochloric acids, furan-3-carboxylic acids are obtained[136,138,139].

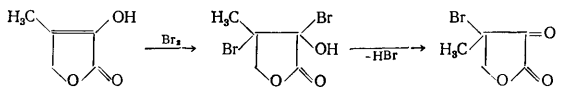
The reaction of Δ$^{\alpha\beta}$-butenolides aith organometallic compounds has been investigated. Δ$^{\alpha\beta}$-Butenolides behave in different ways in reactions with organomagnesium compounds. Thus, when bromomuconic acid is treated with alkylmagnesium halides in ethereal solution, γ-alkyl-αβ-dibromo-Δ$^{\alpha\beta}$-butenolides are obtained[75,154]:



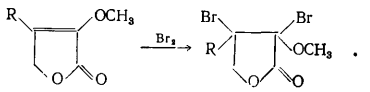
Bromomuconic acid reacts with phenylmagnesium bromide with much greater difficulty[75,154], undergoing a series of transformations: the reaction leads to a magnesium halide alkoxide:



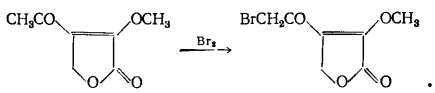
When the final organomagnesium compound is treated with dilute sulphuric acid, cinammic acid derivatives are obtained. The ability of the double bond in Δ$^{\alpha\beta}$-butenolides to undergo electrophilic reactions has also been investigated in relation to halogenation reactions. The latter proceed with retention of the lactone ring. It has been shown[185] that α-hydroxy-β-methyl-Δ$^{\alpha\beta}$-butenolide reacts with an equimolar amount of bromine, forming αβ-dibromo-α-hydroxy-β-methyl-γ-lactone, which splits off one molecule of hydrogen bromide and is converted into β-bromo-β-methyl-α-oxo-γ-lactone:



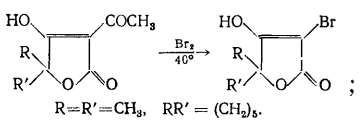
Bromination of β-alkyl-α-methoxy-Δ$^{\alpha\beta}$-butenolides leads to the formation of β-alkyl-αβ-dibromo-α-methoxybutyrolactones[186]:



In the presence of the acetyl group as a substituent, the bromination involves the latter with formation of β-bromoacetyl-α-methoxy-Δ$^{\alpha\beta}$-butenolide:

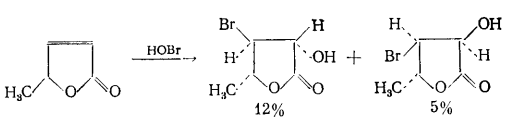


When α-acetyl-γγ-dimethyl- and α-acetyl-γγ-spirocyclohexane-tetronic acids are acted upon by bromine, the acetyl group is split off and the corresponding α-bromo-γγ-dimethyl- and α-bromo-γ-spirocyclohexane-tetronic acids are obtained[156]:



When α-acetyl-Δ$^{\alpha\beta}$-butenolides react with an equimolar amount of phosphorus pentachloride, α-(α-chlorovinyl)-Δ$^{\alpha\beta}$-butenolides are formed, while an excess of phosphorus pentachloride leads to the formation of α-(αβ-dichlorovinyl)-Δ$^{\alpha\beta}$-butenolides[187].

The reaction of β-angelica lactone with hypobromous acid results in the formation (in very low yields) of crystalline diastereoisomers of β-bromo-α-hydroxy-γ-valerolactone[188]:

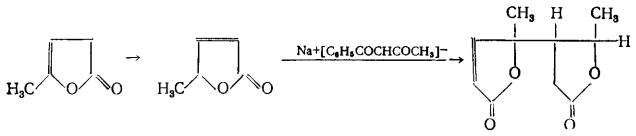


When hydrogen chloride or bromide combines with a Δ$^{\alpha\beta}$-butenolide, the product is β-chloro- or β-bromo-γ-butyrolactone[189]. In the latter case, 3,4-dibromobutyric acid is also formed[189].

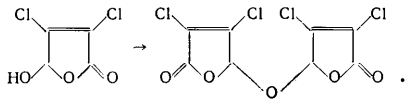
Δ$^{\alpha\beta}$-Butenolides react with diazomethane to form methylated products[34,151,167,190,191]. Thus the reaction of γ-benzylidene-α-methoxycarbonyl-Δ$^{\alpha\beta}$-butenolide with diazomethane yields the corresponding β-methylderivative. *C*-Methylation therefore proceeds more rapidly than the formation of the cyclopropane derivative. γ-Benzylidene-α-cyano-β-methyl-Δ$^{\alpha\beta}$-butenolide has been obtained similarly[151].

β-Angelica-lactone or a mixture of the α- and β-isomers dimerises at 20–200°C in the presence of tertiary amines, alkali metals, or alkali metal alkoxides and hydroxides[192-194]. It has been established that β-angelica lactones are more reactive than their α-isomers. The isomerisation of β-angleica lactones also proceeds in the presence of the sodium salt of benzylacetone or anhydrous potassium

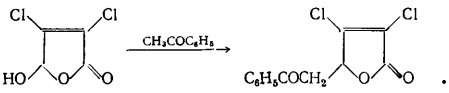
carbonate[195,196]; the authors suggest that the process proceeds as follows:



Dimerisation is also observed when $\alpha\beta$-dichloro-γ-hydroxyangelica lactone is dehydrated by benzenesulphonic acid[70]:

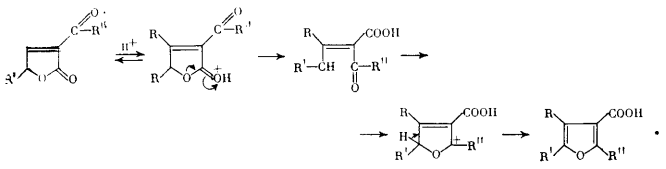


Dieckman and Platz[197] achieved for the first time the condensation of chloromuconic acid and acetophenone in the presence of an aqueous alcoholic solution of alkali, which gave a low yield of $\alpha\beta$-dichloro-γ-phenacyl-$\Delta^{\alpha\beta}$-butenolide:

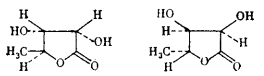


Later it was shown[75] that, when the condensation is carried out in an aqueous alkaline solution, the yield of γ-phenacyl-$\Delta^{\alpha\beta}$-butenolide increases appreciably[75].

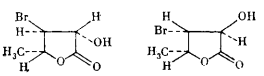
$\Delta^{\alpha\beta}$-Butenolides are readily oxidised by potassium permanganate to dihydroxylactones, which may be hydrolysed to the corresponding trihydroxyacids[103,198]. Thus $\alpha\gamma$-dimethyl-$\Delta^{\alpha\beta}$-butenolide is oxidised to $\alpha\beta$-dihydroxy-$\alpha\gamma$-diphenyl-γ-butyrolactone[199]. However, this reaction pathway is not general since, $\beta\gamma$-diphenyl-$\Delta^{\alpha\beta}$-butenolides, for example, does not form hydroxy-derivatives at all[103]:



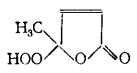
In the presence of osmium tetroxide in an aqueous sodium chloride solution, β-angelica lactone gives rise to a mixture of hydroxylactones[200]:



Stereoisomeric β-bromo-α-hydroxy-γ-valerolactones are formed when β-angelica lactone is treated with hypobromous acid[188]:



β-Angelica lactone also undergoes autoxidation with formation of a hydroperoxy-compound[201]:



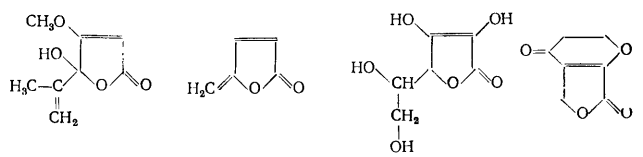
In the presence of silica or pumice at 450–650°C, it is pyrolysed with formation of methyl vinyl ketone[202].

In contrast to their saturated analogues (γ-butyrolactones)[203,204], $\Delta^{\alpha\beta}$-butenolides show little reativity in polymerisation reactions[205-207], but readily copolymerise with various vinyl monomers. Thus the $\Delta^{\alpha\beta}$-butenolide–styrene copolymer has been obtained in the presence of radical initiators[205]. The copolymerisation reactions of $\beta\gamma\gamma$-trialkyl-α-ethoxycarbonyl-$\Delta^{\alpha\beta}$-butenolides with acrylonitrile, *N*-vinylcaprolactam, *N*-vinylpyrrolidinone, methyl acrylate, and vinyl acetate have been investigated[208,209]. The copolymers of α-acetyl- and α-cyano-$\beta\gamma\gamma$-trimethyl-$\Delta^{\alpha\beta}$-butenolides with styrene, acrylonitrile, methyl methacrylate, and *N*-vinylcaprolactam have been obtained[208,209]. The relative activity constants have been determined for certain pairs of monomers[208,209].

Dichloroprotoanemonine also readily copolymerises with vinyl monomers via a radical mechanism[210]. These reactions proceed with retention of the lactone ring and the formation of reactive copolymers.

IV. BIOLOGICAL ACTIVITY OF UNSATURATED γ-LACTONES

The unsaturated lactone ring is present in many natural products[3-6,57,211,212] and physiologically active substances[211-218]. For example, it is a constituent of penicilloic acid, protoanemonine, vitamin C, clavacin, etc:

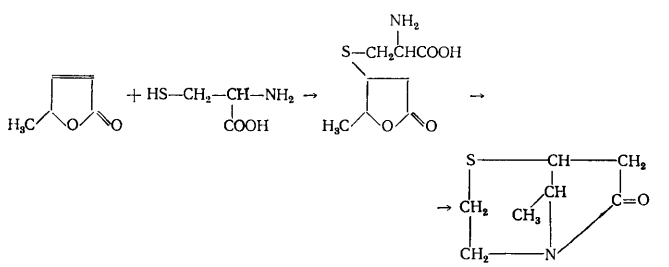


It has been established that the vitamin activity of L-ascorbic acid is due to the presence of the $\Delta^{\alpha\beta}$-butenolide system[211].

Both α- and β-angelica lactones exhibit bactericidal properties[14]. Hydrolysis of the lactone as well as hydrogenation of the double bond entails the loss of activity by these compounds.

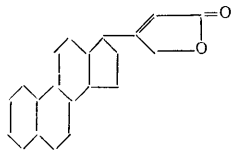
The antibiotic activity of unsaturated lactones has been explained by their ability to react readily with cystine and also with certain enzymes containing mercapto-groups which are important for the normal activity of microorganisms[219-221]. It has been suggested that the bactericidal activity of unsaturated lactones is associated with the ability of the lactone double bond to combine with the SH groups present in bacterial proteins, inhibiting thereby the processes involved in the growth of bacteria[220,221]. A special study has been made of the reaction of cysteine with certain unsaturated lactones, particularly with angelica lactone[220,221].

The reaction proceeds via the mechanism:

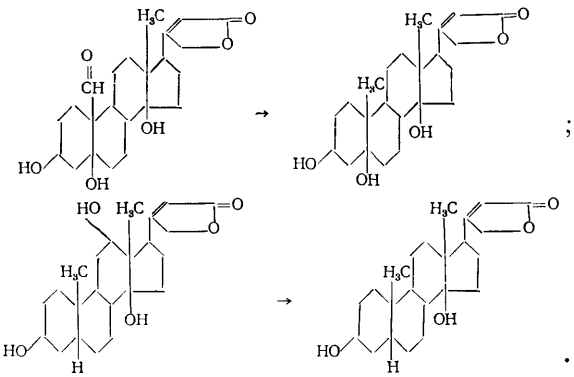


Protoanemonine is an effective antibacterial substance[221].

The class of natural products containing the unsaturated γ-lactone ring, namely natural steroids having the general structure [222-226]

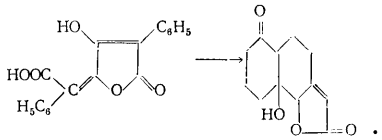


is of interest. Compounds of this type (cardenolides) promote the normal activity of the cardiac muscle in man and animals. Cardenolides are steroids containing a $\Delta^{\alpha\beta}$-butenolide ring in the side chain [223,227-250]. They include for example, strophanthidin, periplogenin, digoxigenin, digitoxigenin, etc:



Cardiac glucosides, incorporating the $\Delta^{\alpha\beta}$-butenolide ring, are present in the cardenolide, the aglycone, or the sugar residue [227].

Vulphinic acid [β-hydroxy-α-phenyl-γ-(phenylcarboxymethylene)-$\Delta^{\alpha\beta}$-butenolide] and ψ-santonin, which exhibits a high physiological activity, also contain the $\Delta^{\alpha\beta}$-butenolide structure [21,251-253]:



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