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γ- and δ-Unsaturated δ-Lactones

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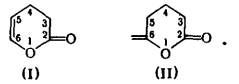
I. INTRODUCTION

Many substances containing unsaturated γ- and δ-lactone rings exhibit physiological activity. It is sufficient to mention the aglycones of cardiac poisons of vegetable and animal origin, various coumarin derivatives, and lactones of the santonin group to have an idea of the importance of compounds of this type.

The varied physiological action of these substances (anthelmintic, effect on heart muscle, ability to arrest the growth of animal tissues and plants), and also the antibiotic activity of the simpler lactones (protoanemonin, parasorbic acid, kawain), are associated with the presence in these compounds of unsaturated lactone rings[1].

These facts are attracting chemists to the study of unsaturated lactones. From the point of view of reactivity, the greatest interest attaches to those in which the double bond is in the vinyl position—either in the ring or outside it—with respect to the heteroatom, this position being responsible for their peculiar chemical behaviour.

Whereas the chemistry of the five-membered unsaturated lactones (but-3(or 4)-en-4-olides) has been developed for many years[2], the principal branches of the chemistry of the six-membered unsaturated lactones (pent-4(or 5)-en-5-olides) have been studied only during the past decade. These investigations have shown wide opportunities for the use of unsaturated δ-lactones in organic synthesis, and have revealed a difference in behaviour between the two types of unsaturated δ-lactones, differing in the position of the double bond—3,4-dihydro-2-pyrones (I) and 6-alkylidenetetrahydro-2-pyrones (II).



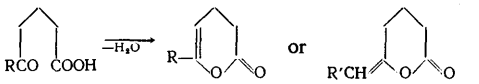
(I) (II)

The present review represents the first attempt to summarise and systematise information on the chemistry of the unsaturated δ-lactones published up to 1966 inclusive.

II. SYNTHESIS OF UNSATURATED δ-LACTONES

1. Dehydration of δ-Keto-acids to Unsaturated δ-Lactones

The chief method of obtaining unsaturated δ-lactones is the cyclodehydration of δ-keto-acids, which can occur in different ways:

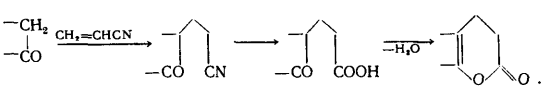


where R = R'CH_2.

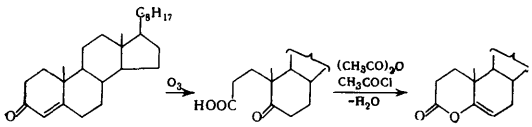
In isolated cases water is eliminated from δ-keto-acids when they are distilled or heated (thermal enol-lactonisation). Since the reaction occurs at a relatively high temperature, this method is used to obtain unsaturated lactones only from keto-acids boiling above 200–250°C.[3-6]

The most important and widely used procedure for the enol-lactonisation of δ-keto-acids† is their dehydration in the presence of acetic anhydride alone[13-23], mixed with acetyl chloride[24,25], or with the addition of catalytic quantities of sodium acetate[26,27], sulphuric acid[6], or perchloric acid[28-30]. This route has been used to prepare δ-lactones having the double bond in the ring (3,4-dihydro-2-pyrones)[30-37] or in the exocyclic position (6-alkylidenetetrahydro-2-pyrones)[4,38,39].

† The possibility of preparing unsaturated δ-lactones in this way is determined mainly by the accessibility of the initial δ-keto-acids, which in turn are synthesised in various ways. Among published general methods of obtaining δ-keto-acids[7-12] the most convenient is the hydrolysis of δ-keto-nitriles[12], which result from the addition of acrylonitrile to ketones. Using this method of synthesising δ-keto-acids, we can pass from ketones to unsaturated δ-lactones in three stages:

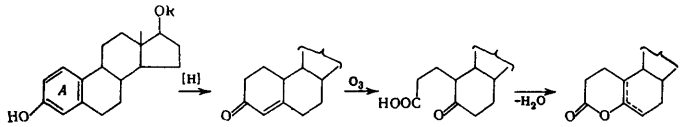


The dehydration of δ-keto-acids is widely used for the preparation of steroid unsaturated δ-lactones. For this purpose the natural steroids are converted by ozonolysis into the δ-keto-acids, which are then lactonised by one of the above methods[25,26]; for example

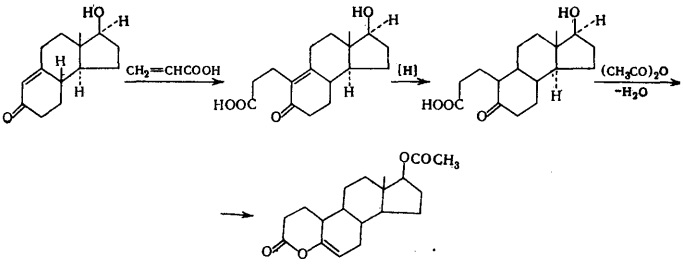


From cholestenone[40-43], testosterone[40,44,45], progesterone[46-49], androsterone and its derivatives[50-52], and cortisone[47,53] have been obtained the corresponding 4-oxasteroids in order to study the physiological action of these lactones, and also to obtain labelled androgens and corticosteroids (see Section III, 3).

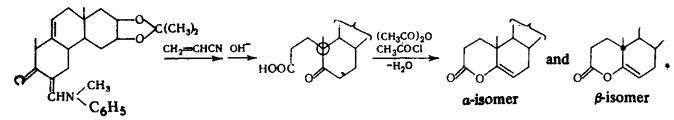
Unsaturated δ-lactones have been obtained also from oestrogens‡, the first stage of the process being in this case reduction of the phenolic ring A to the corresponding unsaturated ketone[54]:



where R = $COCH_3$, COC_6H_5. One of these lactones (with R = $COCH_3$) has been obtained synthetically[55] and then used for the synthesis of 19-nortestosterone:

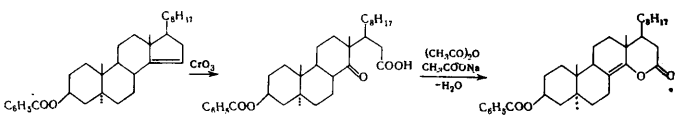


The lactonisation of δ-keto-acids was used by Woodward et al.[26] to prepare tetracyclic unsaturated δ-lactones, which were employed in one of the stages of their total synthesis of steroids:



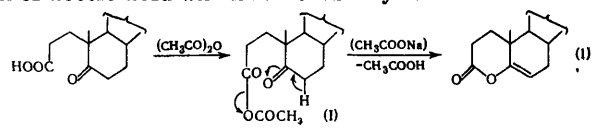
By varying the sequence in which the individual stages in this scheme were accomplished, it then proved possible to obtain predominantly the β-isomer[56-58] (corresponding to the configuration of natural steroids), which, according to Woodward, is obtained in only 13% yield.

In order to obtain a steroid unsaturated δ-lactone in which the D-ring was lactonic, use was made of the δ-keto-acid formed by the oxidation of cholest-14-en-3β-yl benzoate[59]:



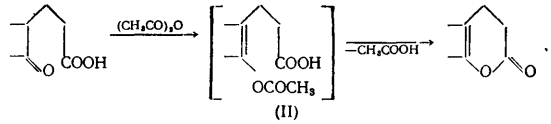
‡ In contrast to the examples given above, the absence of an angular methyl group in position 10 suggests that both isomeric lactones, differing in the position of the double bond, will be formed.

It may be concluded from published data on the mechanism of the action of acetic anhydride in the lactonisation of δ-keto-acids that acylation products are formed initially. But according to Woodward[26] acetic anhydride acylates the carboxyl of the δ-keto-acid to form a mixed anhydride (I)§, from which the unsaturated δ-lactone is obtained by subsequent intramolecular enolacylation of the carbonyl group; the sodium acetate catalyses the elimination of acetic acid which is necessary for this reaction:



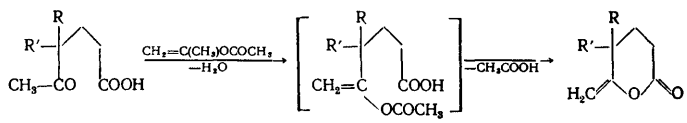
This view of the role of acetic acid is supported by results obtained by Rosenthal et al.[60], who also isolated a mixed anhydride by the action of acetic anhydride on a triterpenoid δ-keto-acid.

However, it may be postulated that the acetic anhydride reacts in a different manner—that it acylates the δ-keto-acid at the carbonyl group with formation of the acetate of the enolic form¶ of the δ-keto-acid (II), subsequent intramolecular reacylation[63,64] of which yields the unsaturated δ-lactone:



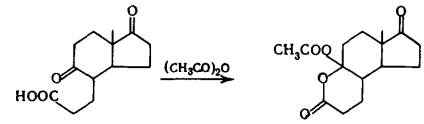
In this case the role of substances of the acidic and basic character of sodium acetate[26], acetyl chloride[25], and sulphuric acid[6], which are used as catalytic additions in enol-lactonisation by means of acetic anhydride, is to facilitate enolisation of the carbonyl group, which is necessary for the reaction to occur in this way. Several authors use scheme (2) to explain the role of acetic anhydride in the lactonisation of δ-keto-acids[65-67].

Scheme (2) also provides an explanation of the anomalous behaviour of γγ-disubstituted δ-keto-acids, which remains unaffected by boiling acetic anhydride[68,69], but are converted into the corresponding unsaturated lactones in 81-99% yield on treatment with isopropenyl acetate:



where R = R′ = CH_3, C_6H_5; R = C_6H_5 and R′ = o-$ClC_6H_4CH_2$. The enolisation of keto-acids containing no γ-hydrogen atom should be difficult, since it can occur only by means of the methyl hydrogen atoms. Therefore the formation of unsaturated acetates of the type (II), which are required

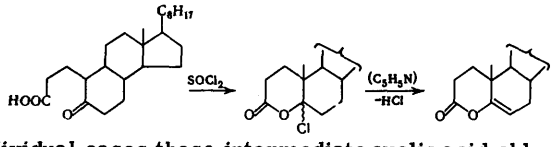
§ On the basis of the infrared spectra Woodward assumed an open-chain structure for the intermediate anhydride (I). More recently, however, it has been shown (from the infrared and nuclear magnetic resonance spectra) that an anhydride of this type obtained from a bicyclic keto-acid has a cyclic structure[27]:



¶ Acetates of the enolic forms of ketones are known to be obtained by the action of acetic anhydride on ketones in the presence of sodium acetate or sulphuric acid[61,62].

for the subsequent production of unsaturated lactones, will take place only in the presence of such a strong acylating reagent as isopropenyl acetate.

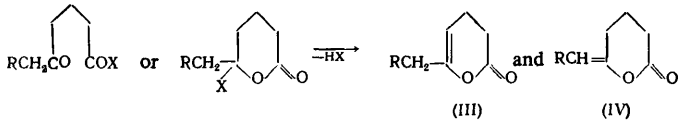
Acid chlorides (acetyl[7,70,71], oxalyl[24], and thionyl[24,72,73]) are widely used for the lactonisation of δ-keto-acids, being more effective than acetic anhydride or phosphorus pentachloride[74]. In this case lactonisation probably involves intermediate formation of the chlorides of the keto-acids, which, as has recently been demonstrated spectroscopically, have (unlike the δ-keto-acids themselves[75]), a cyclic structure[9,76], and readily split off hydrogen chloride[25,45] to form the unsaturated δ-lactones; e.g. [25]



In individual cases these intermediate cyclic acid chlorides have been isolated[9,25,45,54,76-78]. Their properties, which differ from those of ordinary chlorides of carboxylic acids, also confirm their cyclic structure[25,78].

Thus the lactonisation of δ-keto-acids can be accomplished either by their direct dehydration (thermal enol-lactonisation) or by the intermediate conversion of the original acids into acylation products (action of acetic anhydride) or cyclic acid chlorides (action of acid chlorides).

When hydrogen atoms are present in the γ- and ε-positions of δ-keto-acids and their derivatives†, isomeric unsaturated δ-lactones can be obtained, with the double bond either in the ring (III) or in the exocyclic position (IV):



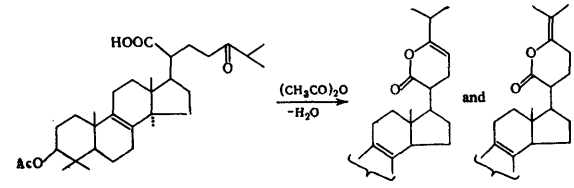
(III) (IV)

where X = Cl, CH_3COO, OH. Which of the isomeric lactones (III) and (IV) is obtained in each individual case is determined either by the direction in which the initial keto-acid undergoes enolisation or by the direction in which HX is eliminated from their cyclic forms[79-83].

Spectral methods have been successfully employed for the investigation of these unsaturated δ-lactones‡. It has been shown that the stretching vibrations of an exocyclic double bond are represented in the infrared spectra of the unsaturated δ-lactones by intense absorption at 1649–1662 cm^{-1},[84,85] whereas the stretching vibrations of an endocyclic double bond in these compounds correspond to extremely weak bands in the range 1695–1710 cm^{-1}.[54,84]

The Raman spectra can also be successfully used to establish the position of the double bond in unsaturated δ-lactones, since they show a difference of the same order as in the infrared spectra for lactones having semicyclic and endocyclic double bonds. However, the intensity of absorption in the region of the carbon–carbon double bond is extremely strong in the Raman spectra for both types of lactones[84].

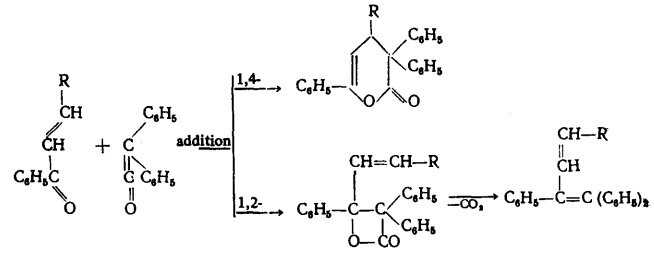
The application of spectral methods of investigation has shown that the simplest δ-keto-acids, whose structure permits the formation from them of both types of unsaturated lactones, are converted predominantly into those containing an endocyclic (more substituted) double bond[84]. Recently, however, examples have been described of the lactonisation of δ-keto-acids of complicated polycyclic structure with the formation of both possible isomers[54,60,91]. Thus the δ-keto-acid obtained by ozonolysis of the triterpenoid eburicoic acid is dehydrated to a mixture of isomeric lactones, the different positions of the double bond in which have been proved by ozonolysis and by the nuclear magnetic resonance spectra[60,91]:



The nuclear magnetic resonance spectra have been used to establish the position of the double bond in other polycyclic unsaturated δ-lactones[5,16,27,60,91,92].

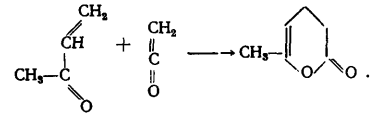
2. Other Syntheses of Unsaturated δ-Lactones

Unsaturated δ-lactones can be synthesised (in 20–30% yield) by Staudinger's method[93]—from ketens and αβ-unsaturated ketones (1,4-addition)—when diene hydrocarbons are also formed, by decarboxylation of the β-lactones produced by 1,2-addition:

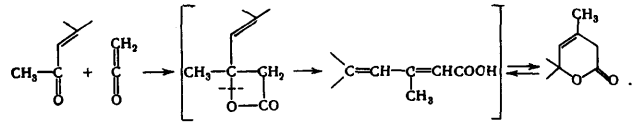


where R = C_6H_5, p-$CH_3OC_6H_4$, p-$(CH_3)_2NC_6H_4$.

The reaction between but-3-en-2-one and keten (the first members of each series) yields only the 1,4-addition product[94]:



Alk-3-en-2-ones react with keten only in the presence of a catalyst (boron trifluoride), forming unsaturated δ-lactones in which the double bond is in the βγ-position. Production of the latter is explained by isomerisation of the β-lactones formed initially by 1,2-addition; e.g.[95]

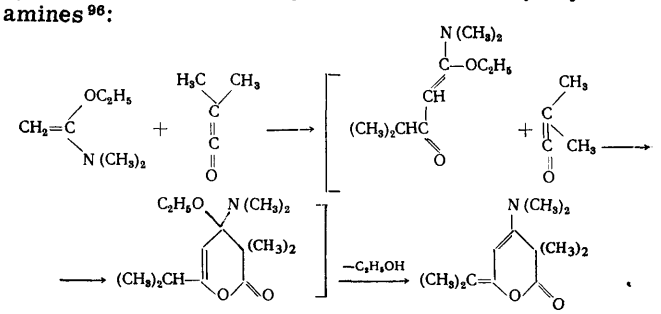


Thus the addition of ketens to αβ-unsaturated ketones takes place in both possible directions in 1,2- or 1,4-positions depending on the structure of both components.

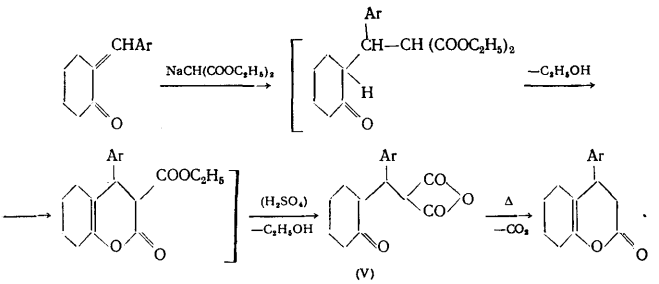
† In contrast to the acid chlorides[25] and anhydrides[27] the δ-keto-acids themselves exist in the open-chain form[75]. However, this fact does not exclude the possibility of their reacting in their cyclic form during lactonisation.

‡ The infrared and Raman spectra of these unsaturated δ-lactones exhibit an intense carbonyl absorption in the range 1750–1780 cm^{-1},[84,85,87,88] which distinguishes them from unsaturated δ-lactones in which the double bond is in the αβ- or βγ-position (carbonyl absorption at 1710–1730 cm^{-1}) and from 2-pyrones (1720–1740 cm^{-1}).[86,89,90]

δ-Lactones containing an exocyclic double bond can be synthesised from dimethylketen§ and 1-alkoxyvinylamines[96]:

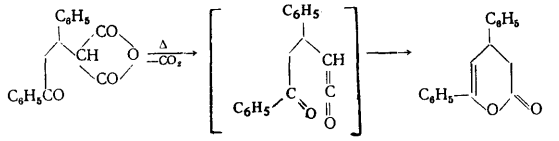


The condensation of benzylidene- and *p*-methoxybenzylidene-cyclohexanone with sodiomalonic ester (the Michael reaction)[98] yielded unsaturated α-ethoxycarbonyl-δ-lactones, which were easily further converted into substituted γ-keto-malonic anhydrides, the latter again being cyclised (on heating) into unsaturated δ-lactones:

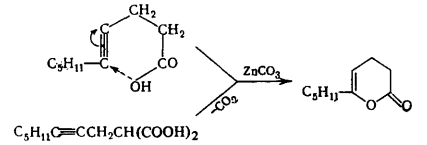


(V)

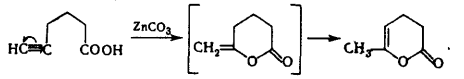
A similar conversion of γ-keto-malonic anhydrides (V)¶ into unsaturated δ-lactones was observed by Mannich and Butz[17], who regarded this reaction as an intramolecular enolacylation of an anhydride keto-group. It may be supposed, however, that under these conditions acylation will be effected by ketens formed as intermediates†, which, according to Staudinger's results[99], are readily obtained from such malonic anhydrides on heating; e.g.



Unsaturated δ-lactones are formed also by the cyclisation of pent-4-ynoic acid or the corresponding prop-2-ynylmalonic acids under the influence of zinc carbonate[100]; e.g.

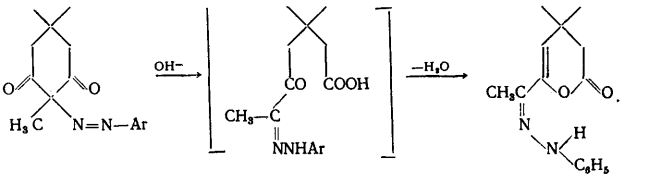


Under these conditions hex-5-ynoic acid could be expected to yield a δ-lactone containing an exocyclic double bond. However, the double bond migrated into the ring, and 3,4-dihydro-6-methyl-2-pyrone was obtained:

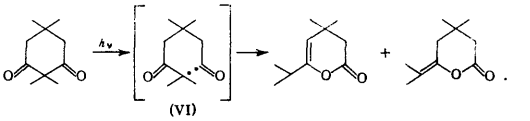


In spite of the comparatively good yields (45–65%) of unsaturated δ-lactones, application of this method is restricted by the relative inaccessibility of the initial alkynoic acids.

Unsaturated δ-lactone rings are formed by the alkaline hydrolysis of azo-derivatives of cyclohexane-1,3-diones (obtained by the Japp–Klingemann method); e.g.[101]



The photoisomerisation has recently been described of 2,2,5,5-tetramethylcyclohexane-1,3-dione (on exposure of a benzene solution) into a mixture of δ-lactones containing an exocyclic or an endocyclic double bond (in 92% and 1.3% yield respectively)[102]:



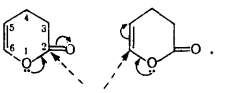
(VI)

This interesting reaction probably involves the intermediate formation of a diradical (VI), which then cyclises into an unsaturated lactone.

III. REACTIONS OF UNSATURATED δ-LACTONES

Unsaturated δ-lactones are highly reactive; in many respects their activity is similar to that of vinyl esters—of which they are cyclic analogues—and of unsaturated γ-lactones[2].

Like these compounds, unsaturated δ-lactones react readily with nucleophilic reagents. Since the distribution of electron density in the unsaturated lactones is such that the ring carbon atoms 2 and 6 are positively charged, it can be expected that attack by nucleophilic reagents will take place at one of these carbon atoms, with subsequent cleavage of the 1–2 or the 1–6 bond and formation of two series of derivatives (as occurs with 2-pyrones)[97]:



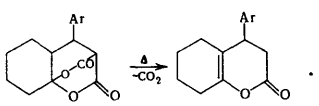
Unsaturated δ-lactones react readily also with electrophilic reagents, forming products of addition at the double bond, which possesses enhanced nucleophilic character in unsaturated lactones (as also in vinyl ethers).

1. Hydrolysis, Alcoholysis, and Ammonolysis

Unsaturated δ-lactones react readily‡ with water, the

§ Use of keten itself in this reaction[97] yields 2-pyrones.

¶ These substances may have the structure of the isomeric dilactones[98], which on decarboxylation also give the corresponding δ-lactones:

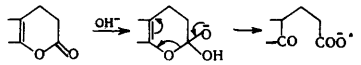


† The formation of these ketens (not the unsaturated lactones) was expected by Mannich and Butz[17], when investigating the behaviour of malonic anhydrides on heating.

‡ Some hydrolysis of unsaturated δ-lactones occurs even under the influence of atmospheric moisture[30,103].

lactone ring being opened and δ-keto-acids being formed.

Alkaline hydrolysis takes place still more easily, and leads (often in the cold) to the formation of quantitative yields of salts of the δ-keto-acids:

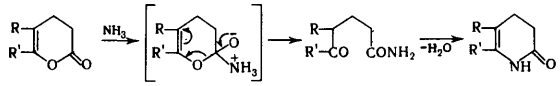


However, the ease of ring opening on alkaline hydrolysis may vary greatly with the nature and position of substituents in the unsaturated δ-lactone and with the strength of the base employed[13,15,17,49,93].

Acid hydrolysis has been described only in the case of one unsaturated lactone, which contained a 4-amino-group[96].

The reaction between unsaturated δ-lactones and alcohols, which results in the formation of esters of δ-keto-acids, also requires the presence of alkaline or acidic catalysts (in the absence of a catalyst the reaction goes very slowly on prolonged heating[17]). The ease of alcoholysis in the presence of acids is, perhaps, explained by protonation of the double bond in the lactone, resembling what occurs in the alcoholysis of vinyl esters[104]. This reaction is used for the preparation of esters of δ-keto-acids[4,31,34,35,68,105].

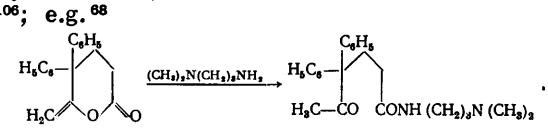
The action of ammonia on unsaturated δ-lactones leads to opening of the ring at the 1–2 bond§ with the formation of δ-keto-amides. Depending on their structure, the latter can be dehydrated with varying ease into the corresponding 5,6-unsaturated lactams (the nitrogen analogues of the δ-lactones)[3,13,17,34,35,38,93,106–108]; e.g.[107]



where R = C_2H_5 and R′ = C_6H_5.

The conversion of steroid unsaturated δ-lactones into the corresponding unsaturated δ-lactams (by the action of ammonia) provided a new method for the synthesis of azasteroids[51,109–111].

With amines unsaturated δ-lactones give high yields (usually in the cold) of substituted δ-keto-amides[13,17,68–74,103,106]; e.g.[68]



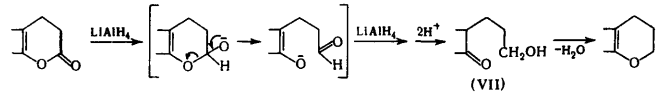
These examples show that unsaturated δ-lactones react with water, alcohols, ammonia, and amines under far milder conditions than do saturated δ-lactones. The reactions of hydrolysis, ammonolysis, and alcoholysis, resulting in the formation of δ-keto-acids and their derivatives, are used for the identification of unsaturated δ-lactones.

2. Reduction with Lithium Tetrahydroaluminate

Recent investigation of the reactions undergone by unsaturated δ-lactones with lithium tetrahydroaluminate has shown that various reduction products are formed depending on the position of the double bond.

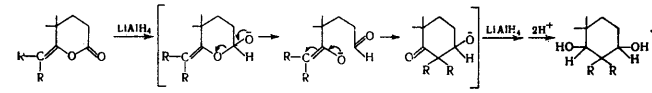
§ Addition at the 1-6 bond should have resulted in the formation of δ-amino-acids, but the latter were not observed in these cases.

Unsaturated δ-lactones containing a cyclic double bond (3,4-dihydro-2-pyrones) are reduced to 5-hydroxyalkanones (VII), which on dehydration readily undergo cyclisation to dihydropyrans[112]:



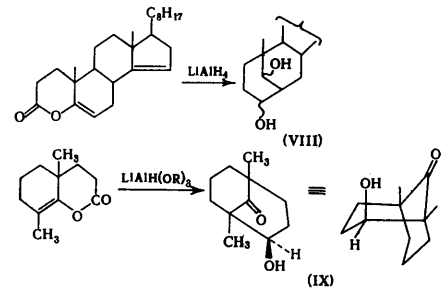
(VII)

Unsaturated δ-lactones containing an exocyclic double bond (6-alkylidenetetrahydro-2-pyrones) are reduced by lithium tetrahydroaluminate to cyclohexane-1,3-diols (in 52–65% yield), with rearrangement[113]:



where R = H, CH_3.

The reduction of δ-lactones whose exocyclic double bond forms part of a ring fused with the lactone ring yields bridged compounds. Thus 4-oxacholest-5-en-3-one is converted under the influence of lithium tetrahydroaluminate into the bridged diol (VIII)¶ [114], whereas the action of lithium hydrotri-t-butoxyaluminate on a bicyclic lactone of similar structure yields an incompletely reduced product, the hydroxy-ketone (IX)[115]:



(VIII)

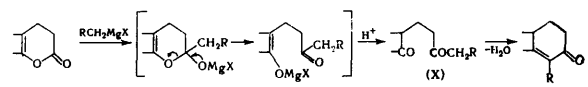
(IX)

Martin et al.[116] have shown that in the last example the reaction goes stereospecifically with formation of the epimer having the hydroxyl in the axial position (IX).

3. Reaction with Organomagnesium Compounds

δ-Lactones which differ in the position of a double bond behave differently with organomagnesium compounds.

3,4-Dihydro-2-pyrones (lactones having the double bond in the ring) add one or two moles of Grignard reagent depending on the conditions. When the reactants are added in the reverse order in the proportions 1 : 1 at −20°C, one mole of the organomagnesium compound is added. The reaction products are 1,5-diketones (X), which are further converted by intramolecular aldol condensation into cyclohex-2-enones[117]:

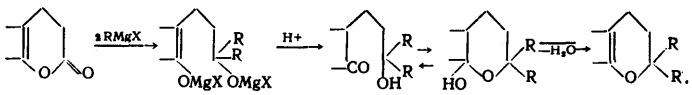


(X)

With excess of the organomagnesium compound at temperatures above 0°C, two moles thereof are added, the

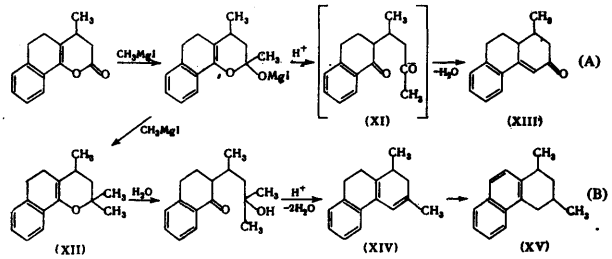
¶ The product of the reduction of this lactone by lithium tetrahydroaluminate had earlier been erroneously attributed the structure 3,5-seco-cholestane-3,5-diol[43].

main reaction products[118] being 3,4-dihydropyrans (yield 47–80%):

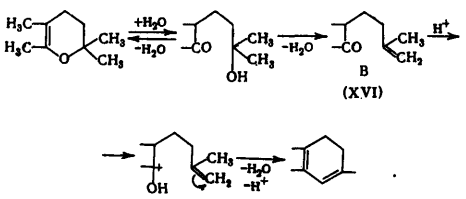


The reaction can be utilised for the preparation of substituted dihydropyrans.

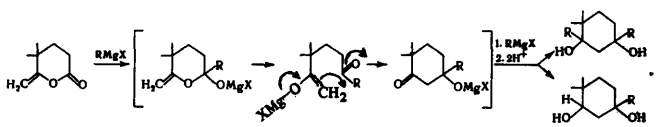
Similar observations were made by Belleau[24]. However, the reaction products formed initially—the diketone (XI) and the dihydropyran (XII)—were converted under the conditions of hydrolysis into respectively the unsaturated ketone (XIII) and the cyclohexadiene hydrocarbon (XIV), the latter of which immediately isomerised into the hydrocarbon (XV). These changes were explained by the scheme



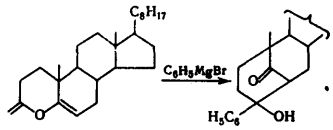
Formation of cyclohexadiene hydrocarbons by the hydrolysis of substituted dihydropyrans has been observed by the present reviewers[119], who showed that, contrary to Belleau's scheme, these hydrocarbons were formed as a consequence of intramolecular cyclisation of δε-unsaturated ketones (XVI) formed from the dihydropyrans; e.g.



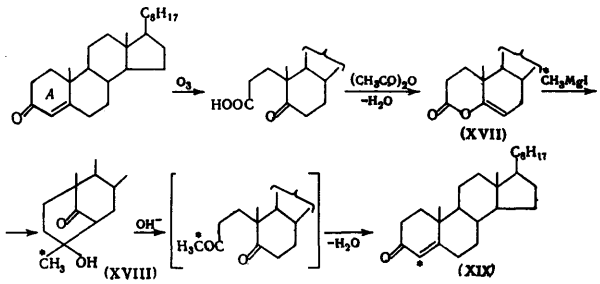
The action of organomagnesium compounds of δ-lactones containing an exocyclic double bond results in the formation of cyclohexane-1,3-diols[120], whose appearance is explained by a rearrangement resembling that described above in the reduction of unsaturated lactones with lithium tetrahydroaluminate; e.g.



Rearrangement accompanies also† the reaction of organomagnesium compounds with steroid δ-lactones containing an exocyclic (with respect to the lactone ring) double bond. In this case the reactions terminate at the stage of formation of bridged hydroxy-ketones[123,124] (reaction products of this type had earlier been regarded erroneously as 1,5-diketones and hemiacetals[40,41]); for example



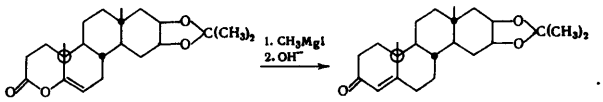
The interaction of organomagnesium compounds with steroid unsaturated lactones has been described in many papers. Thus Fujimoto[40] used this reaction to develop a method for introducing labelled carbon into position 4 in ring A of testosterone and cholestenone. The action of methylmagnesium iodide on the unsaturated lactone (XVII) (obtained from natural cholestenone) produces a bridged hydroxy-ketone (XVIII), which is then converted (by treatment with alkali) into cholestenone (XIX), which is identical with the natural product[40]:



It is obviously possible by means of this series of reactions to break down and recreate ring A of the steroid. In this way, with the use of methylmagnesium iodide containing labelled carbon, the latter can be introduced into position 4 of ring A. This scheme of Fujimoto's served (without isolation of the intermediate hydroxy-ketone of type (XVIII) for the preparation of many ^{14}C-labelled steroids for the study of their metabolism. Cholestenone[41], progesterone[46,47], and 17-hydroxy-17α-methylandrost-4-en-3-one[51] have been obtained in this way.

Fujimoto's scheme can be used also to introduce an alkyl group into the 4-position of the steroid ring system by bringing other alkylmagnesium halides into reaction with steroid unsaturated lactones. Various 4-methylated steroids—4-methylcholestenone[42,125,126], 17-hydroxy-4-methylandrost-4-en-3-one[44,125,126], 17-hydroxy-4-methyl-19-norandrost-4-en-3-one[126], and also 4-ethyl-17-hydroxyandrost-4-en-3-one[126]—have thus been prepared with the aim of studying their androgenic activity. The acetates of 17-hydroxy-4-methyl-19-norandrost-4-en-3-one[54,92] and 4-methylhydrocortisone[127] have been synthesised in a similar manner.

The reaction between unsaturated lactones and organomagnesium compounds was used by Woodward[26] to build up the ring A in his total synthesis of steroids:



The stereospecificity which he observed in the Grignard reaction with lactones differing in configuration at $C_{(10)}$ served for the separation of α- and β-epimers and confirmed their configuration[56,57,128].

Thus the reaction between unsaturated δ-lactones containing an exocyclic (relative to the lactone ring) double bond and organomagnesium compounds has been widely

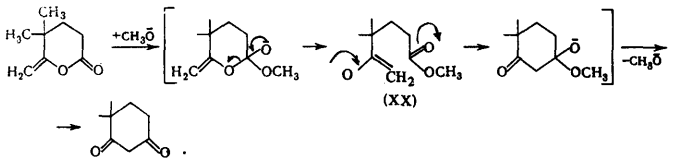
† It was found that rearrangement also accompanied reaction of the linear analogues of unsaturated δ-lactones—vinyl esters—with organomagnesium compounds[121]. The acetate of the enolic form of cyclohexanone, however, reacts normally[122].

used for various synthetic purposes—to prepare cyclohexane-1,3-diols, for the synthesis of 4-methylated steriods containing labelled carbon, and also in the complete synthesis of steroids.

4. Isomerisation of Unsaturated δ-Lactones in the Presence of Sodium Alkoxides

When heated with sodium ethoxide (for 2–10 h), unsaturated δ-lactones isomerise‡ into cyclohexane-1,3-diones[129,130].

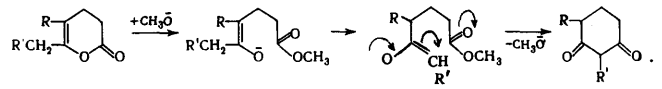
With unsaturated δ-lactones containing an exocyclic double bond (e.g. tetrahydro-5,5-dimethyl-6-methylene-2-pyrone) this transformation is explained by the scheme



(XX)

The anion (XX) is then cyclised by a kind of intramolecular Claisen condensation and is converted into the corresponding cyclohexane-1,3-dione.

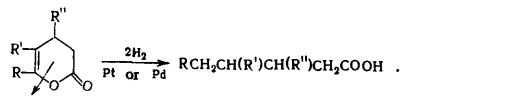
Lactones containing an endocyclic double bond are also converted, when heated with sodium methoxide, into the corresponding cyclohexane-1,3-diones. In this case the double bond probably migrates from the γδ- to the δε-position[130]:



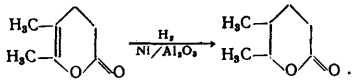
The isomerisation of unsaturated δ-lactones in the presence of sodium methoxide can be utilised for the preparation of cyclohexane-1,3-diones.

5. Catalytic Hydrogenation of Unsaturated δ-Lactones

In the presence of catalysts one or two molecules of hydrogen can be added to unsaturated δ-lactones, with the formation respectively of saturated lactones and saturated acids. Lactones containing a double bond in the ring are hydrogenated in the cold§ over platinum or palladium with the formation solely of carboxylic acids[30,131,132]:

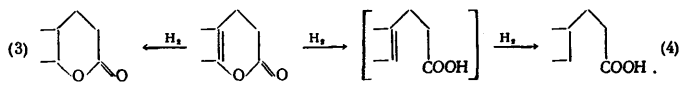


This hydrogenolysis is the only example of the opening of the unsaturated δ-lactone ring at the 1–6 bond. The hydrogenation of lactones of this type over nickel on aluminium oxide in a flow system at 200°C led to the formation of a saturated lactone¶; for example[31]

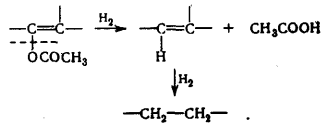


Lactones containing an exocyclic double bond are hydrogenated over a platinum catalyst (in the cold) in both possible ways[25,31].

Thus the hydrogenation of unsaturated δ-lactones can occur simultaneously in two ways—at the double bond with formation of a saturated lactone (3) and at the 1–6 bond of the lactone ring with subsequent hydrogenation of the resulting unsaturated acid (4)—the relative rates of these reactions, determined by the structure of the δ-lactone and the conditions of hydrogenation, governing the formation of the final reaction products:



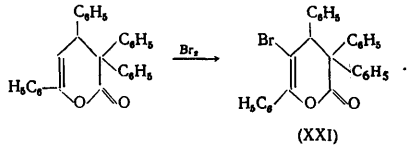
It is interesting that hydrogenation of the linear analogues of the unsaturated lactones—enolic acetates—probably occurs in the second way (hydrogenolysis of the ester bond followed by hydrogenation of the double bond)[137]:



6. Halogenation of Unsaturated δ-Lactones

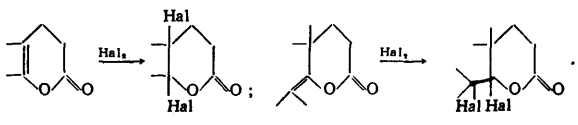
The properties of the double bond in unsaturated δ-lactones, which by analogy with vinyl esters should possess enhanced nucleophilic character, have been studied only with respect to halogenation. The lactone ring is preserved during these reactions.

Staudinger[93] brominated 3,4-dihydro-3,3,4,6-tetraphenyl-2-pyrone, obtaining a monobromo-derivative to which he attributed without proof the structure of a brominated unsaturated lactone (XXI):



(XXI)

A detailed study of the halogenation of unsaturated δ-lactones was made by Levina, Shusherina, and their collaborators[138–141], who showed that in the cold bromine[138,142] or chlorine[141] (by the action of sulphuryl chloride†) is readily added at the double bond to form reactive dihalides:



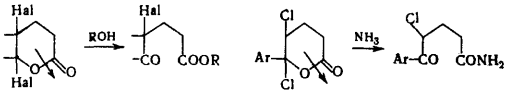
‡ Brief action of sodium ethoxide (in the cold) on unsaturated δ-lactones followed by treatment with water yields esters of δ-keto-acids[53].

§ Unsaturated δ-lactones containing the double bond in the αβ- or βγ-position add hydrogen only at the double bond under the same conditions[95,133]. Endeavours have been made to utilise this difference in behaviour between lactones containing the double bond in different positions to establish the structure of naturally occurring compounds containing an unsaturated lactone ring[134,135].

¶ An attempt to explain the formation of saturated acids by hydrogenolysis of initially formed saturated lactones[131] proved to be untenable[136].

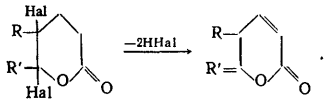
† The action of chlorine on unsaturated δ-lactones involves not only addition at the double bond but also replacement of hydrogen.

The dihalides react with water, alcohols[142-145], and ammonia[146] with opening of the lactone ring and formation of γ- and ϵ-halogenated δ-keto-acids, their esters, and their amides (in 70–100% yield):



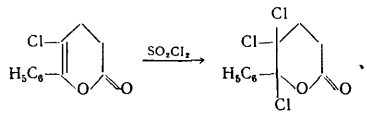
where Hal = Cl, Br and R = H, Alk.

On distillation dihalogenolactones, as well as the trihalogenolactones obtained from them by further halogenation, undergo partial[148] or complete[138,139] dehydrohalogenation, during which the lactone ring is preserved:

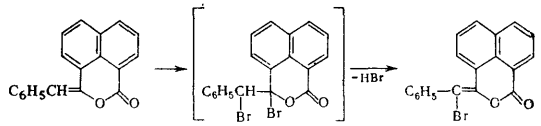


These reactions of the indirect dehydrogenation‡ of unsaturated δ-lactones (involving stages of halogenation and subsequent dehydrohalogenation) provide convenient routes for obtaining difficultly accessible 2-pyrones of various structures[138-141,147-149], including those containing a 5-bromo-substituent or a 6-bromomethyl group.

It is interesting that the nucleophilic character of the double bond is diminished in 5-chloro-3,4-dihydro-2-pyrones. They do not react at all with bromine in the cold, though they add chlorine at the double bond[150]:

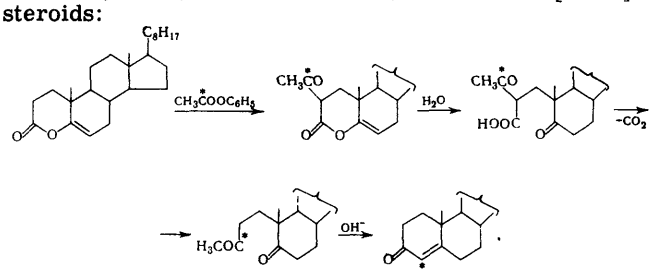


A brominated lactone containing an exocyclic double bond was obtained by the bromination of 3-benzylidenenaphthalide[151]:



7. Reactions of the α-Methylene Group

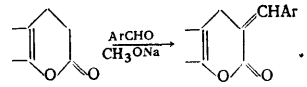
In the presence of sodium hydride the steroid unsaturated δ-lactones obtained from cholestenone and testosterone react as the methylene component in the aldol condensation with phenyl acetate[25]. When labelled phenyl acetate was used, the resulting acylated unsaturated lactones were converted (through the stages of hydrolysis, decarboxylation, and condensation) into labelled [4-^{14}C] steroids:



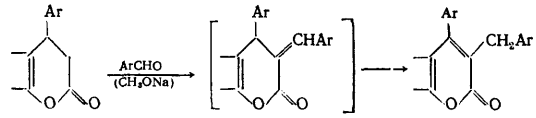
‡ The direct dehydrogenation of unsaturated δ-lactones to 2-pyrones—in boiling cymene over palladium on carbon—has been described only in the case of a triterpenoid unsaturated lactone[60].

This route has been used also to obtain labelled progesterone[49].

Unsaturated δ-lactones condense with aromatic aldehydes in the presence of sodium methoxide[152] to form 3-benzylidene-3,4-dihydro-2-pyrones:

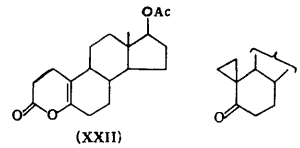


2-Pyrones can be obtained by means of this reaction from unsaturated lactones containing a 4-aryl substituent, since the benzylidene derivatives formed as intermediates immediately isomerise into 3-benzyl-2-pyrones:



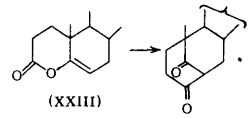
8. Photolysis of Unsaturated δ-Lactones

Interesting results have been obtained by the ultraviolet irradiation of unsaturated δ-lactones. The steroid δ-lactones (XXII) containing an endocyclic double bond was converted under these conditions into the corresponding cyclopropyl ketone in 40% yield[135]:



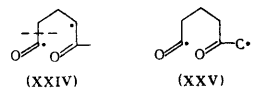
(XXII)

The lactone (XXIII) containing an exocyclic double bond isomerised into a bridged diketone (cf. isomerisation of unsaturated δ-lactones into 1,3-diketones in the presence of sodium methoxide, subsection 4)[153]:



(XXIII)

The most probable mechanism of isomerisation is that the diradical (XXIV), resulting from the lactone (XXII), is then stabilised by the elimination of carbon monoxide with formation of a three-membered ring; the diradical (XXV), formed from the lactone (XXIII), is stabilised as the dicarbonyl compound:



(XXIV) (XXV)

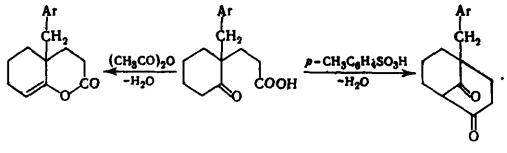
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The above survey makes it clear that investigations during recent years have revealed the great reactivity of unsaturated δ-lactones. The two main types of reactions studied (with preservation and with cleavage of the lactone ring) exhibit the peculiarities of the chemical behaviour of these compounds, which are determined by the vinyl position of the double bond relative to the heteroatom.

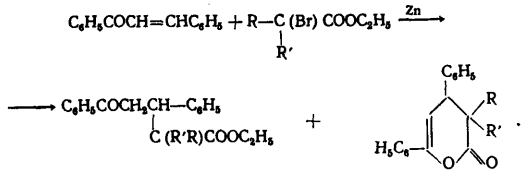
---o0o---

Papers have appeared since this review was submitted for publication which must be considered, if only very briefly, since they are directly concerned with the subject-matter of the present survey.

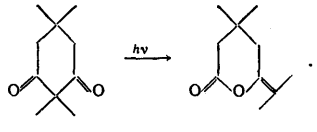
The lactonisation of δ-keto-acids has been described by the action of acetic anhydride[154,155], by the action of this reagent containing added toluene-*p*-sulphonic acid, and also by heating with toluene-*p*-sulphonic acid in tetralin solution[156]. The last method of dehydration, which was applied to β-(1-benzyl-2-oxocyclohexyl)propionic acids, led unexpectedly to the formation of bridged diketones, whereas the action of acetic anhydride on these keto-acids yields the normal dehydration products—unsaturated δ-lactones[157]:



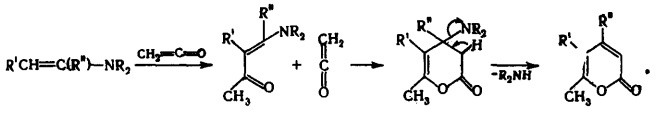
Unsaturated δ-lactones have been obtained from the Reformatsky reagent and αβ-unsaturated ketones, by spontaneous cyclisation of the δ-keto-esters formed directly[158]:



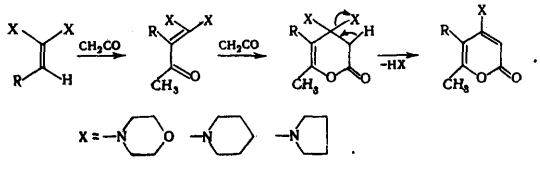
The photochemical conversion has been described of a substituted cyclohexane-1,3-dione into a δ-lactone containing an exocyclic double bond (the reverse reaction to the isomerisation of unsaturated δ-lactones into 1,3-diketones described in Section III, subsections 4 and 8)[159]:



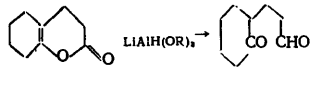
Unsaturated δ-lactones can be obtained by the interaction of acylated enamines with keten, and are easily further converted into 2-pyrones[160]:



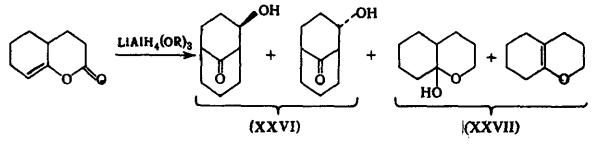
Keten reacts similarly with 1,1-diaminoethylenes to form unsaturated 4,4-diamino-lactones[161]:



Martin et al.[116] have shown that 3,4-dihydro-5,6-cyclohexano-2-pyrone is reduced by lithium hydrotri-t-butoxyaluminate to a δ-keto-aldehyde (without rearrangement of the carbon skeleton—cf. Section III, 2):



whereas the isomeric lactone containing an exocyclic (relative to the lactone ring) double bond will give under these conditions a mixture of reduction products obtained with (XXVI) and without (XXVII) rearrangement of the carbon skeleton (cf. Section III, 2):



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