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PROGRESS IN THE CHEMISTRY OF 2-PYRONES

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I. INTRODUCTION

Many physiologically active compounds contain an α-pyrone ring in their molecule. They include the bufadienolides — heart glycosides of plant and animal origin (bufotalin, cinobufagin, scilliroside, etc.[1-11]), individual representatives of 2-pyrones[12-15] (paracotoin, yangonin, hispidin) which exhibit antibiotic and fungicidal action[16].

In this connection investigations have appeared in the last decade devoted to the development of general methods of synthesis of 2-pyrones, and also the isolation of individual representatives of 2-pyrones from plants and the establishment of their structure.

Derivatives of 2-pyrone were used recently for the synthesis of colchicine[17,18], barrelene[19], and other difficultly accessible compounds.

The present review gives an account of the principal literature on methods of synthesis and the reactivity of 2-pyrones†, indicating the progress in the chemistry of these heterocyclic compounds‡.

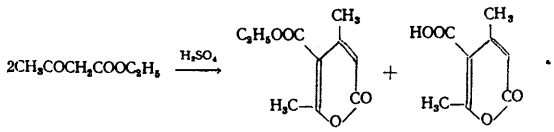
II. METHODS OF SYNTHESIS OF 2-PYRONES

The known methods of synthesis of 2-pyrones can be divided into two types: synthesis from compounds with an open chain of carbon atoms, and from compounds which already contain a six-membered lactone ring.

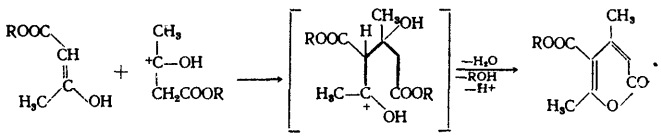
1. CONDENSATION OF β-KETO-ACIDS, β-ALDEHYDO-ACIDS, AND THEIR ESTERS

Condensation in the Presence of Acid Catalysts

One of the longest known methods of synthesis of 2-pyrones is the intermolecular condensation of acetoacetic ester under the action of concentrated sulphuric acid[23] or hydrogen chloride[24-27].

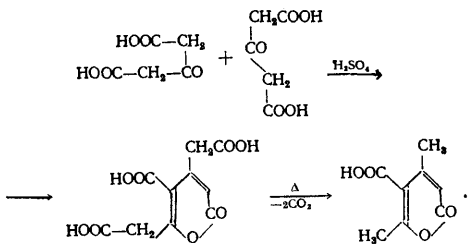


This synthesis of isodehydracetic (2,4-dimethyl-2-oxopyran-5-carboxylic) acid§ and its ester was later studied in detail by Wiley and Smith[28]. According to their suggested mechanism, one molecule of the acetoacetic ester reacts in the enol and the other in the keto- (protonated) form[28]:



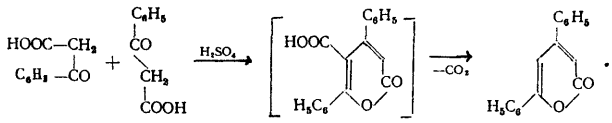
Homologues of isodehydracetic acid and its ester exhibiting bactericidal activity were synthesised in a similar manner[14].

Dibasic β-keto-acids behave analogously in this reaction[34,35]:

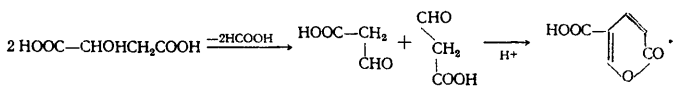


When isodehydracetic acid is heated with concentrated sulphuric acid to 160–170° it is decarboxylated into 4,6-dimethylpyran-2-one[23,36].

Isodehydrobenzoylacetic acid is decarboxylated even at room temperature, therefore the final product of the condensation of benzoylacetic acid is 4,6-diphenylpyran-2-one[37]:



The synthesis of coumalic acid (2-oxopyran-5-carboxylic acid) by heating malic acid with concentrated sulphuric acid and zinc chloride (quantitative yield) apparently proceeds through the stage of formation of a β-aldehydo-acid (the semi-aldehyde of malonic acid), which, like the β-keto-acids, undergoes intermolecular condensation[38,39]:



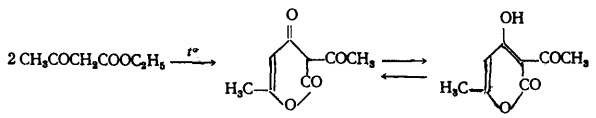
† The literature on the chemistry of the coumarins (benzo[*b*]pyran-2-ones), which exhibit specific properties, is not discussed here.

‡ Cavalieri's review[20] on the chemistry of the pyrones, published in 1947, is out of date. The information about the 2-pyrones given in the monographs edited by Elderfield[21] and by Grignard[22] are also restricted to 1947.

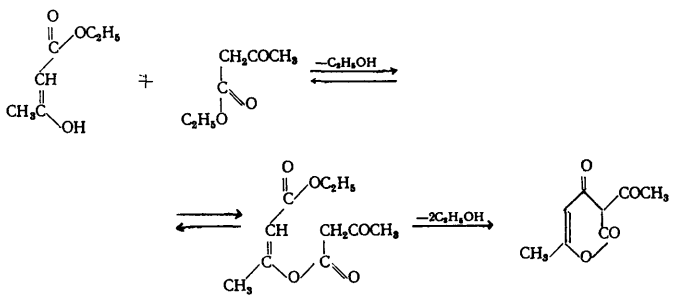
§ Isodehydracetic acid can serve as the starting point for the synthesis of various compounds which are not readily accessible[29,30]; its derivatives are also interesting because of their physiological activity.[31-33]

Condensation in the Presence of Basic Catalysts

Among the thermal decomposition products of acetoacetic ester a substance[40] which received the name dehydracetic acid was observed; later it was ascribed the structure 3-acetyl-6-methylpyran-2,4-dione, which can be found in equilibrium with the tautomeric 3-acetyl-4-hydroxy--6-methylpyran-2-one[41]:

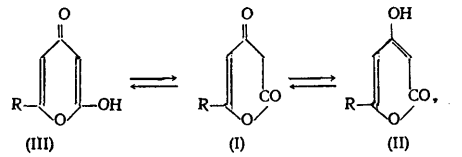


Arndt and coworkers[42-44] suggested that during the pyrolysis a vinyl ester is first formed, which then cyclises into dehydracetic acid (the part of catalyst is played mainly by the walls of the glass reaction vessel):



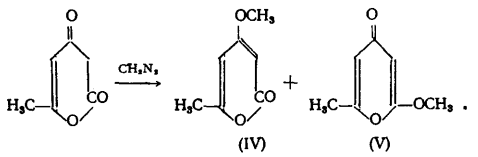
Esters of other β-keto-acids gave in this way alkyl-[45,46], cycloalkyl-[47,48], and aryl-substituted dehydracetic acids[49,50] (some of these compounds exhibit high antibactericidal activity[45,46]).

A notable feature of the compounds of the dehydracetic acid type is their ability when heated with sulphuric acid¶ to lose an acyl group and form 6-substituted pyran--2,4-diones (I)[41-43,52-54]. It is suggested that the latter may exist in two enolic forms — 4-hydroxypyran-2-one (II) and 2-hydroxypyran-4-one (III)[55,56]:

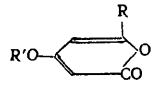


Actually, as infrared and ultraviolet spectra have shown, pyrandiones (pyronones) exist in the form of the 4-hydroxypyran-2-one (II), or the 2-hydroxypyran-4-one (III), or as an equilibrium mixture of (II) and (III), depending upon the substituents, the state of aggregation, and the solvent[57-59].

In the methylation of 6-methylpyran-2,4-dione (and also its analogues) two esters (IV) and (V) were isolated, corresponding to the two possible enol forms[58-65]:



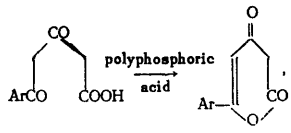
Note that the pyronone nucleus enters into the composition of many physiologically active compounds isolated from plants: yangogin (VI)[66,67], anibine (VII)[68-71], 4-methoxyparacotoin (VIII)[68,70,72], 5,6-dehydrokawain (IX)[72], and hispidin (X)[73,74]:

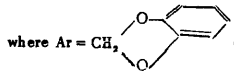


where R′ = CH_3, R = *p*-$CH_3OC_6H_4CH{=}CH$ (VI); 3-C_5H_4N (VII); 3′,4′-$(CH_2O_2)C_6H_3$ (VIII); $C_6H_5CH{=}CH$ (IX); R′ = H, R = 3′,4′-$(HO)_2C_6H_3CH{=}CH$ (X).

2. INTRAMOLECULAR CYCLISATION OF αδ- AND βδ-DIKETO--ACIDS

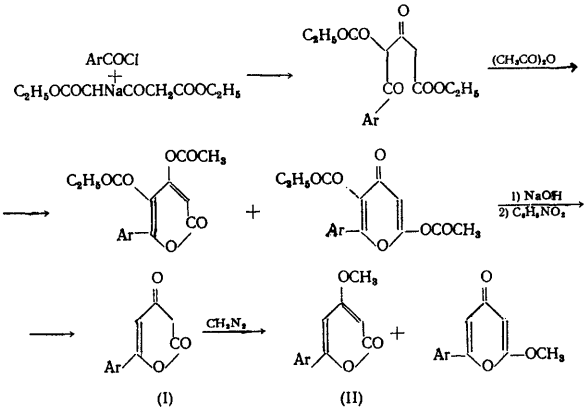
Intramolecular dehydration of βδ-diketo-acids leads to the formation of pyran-2,4-diones. Thus the cyclisation of δ-aryl-βδ-diketovaleric acids under the action of polyphosphoric acid (PPA) gives 6-arylpyran-2,4-diones:





where Ar = CH_2 (Ref. 75), or C_6H_5 (Ref. 76).

The cyclisation of the corresponding ester of a βδ-diketo-acid is the principle of a method by which Borsche first synthesised yanganolactone (I) and from it yangonin (II)†[67]:



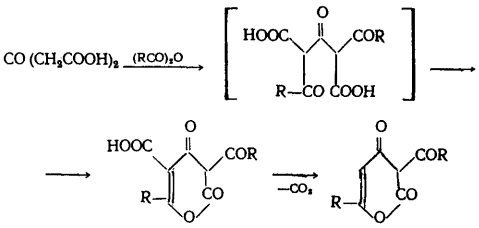
where Ar = *p*-$CH_3OC_6H_4CH{=}CH$.

The cyclisation of βδ-diketo-acids into pyran-2,4-diones sometimes takes place very easily even under conditions

¶ Under the action of hydrohalogen acids dehydracetic acid and its analogues are converted into 2,6-disubstituted 4-pyrones.[41-43,51]

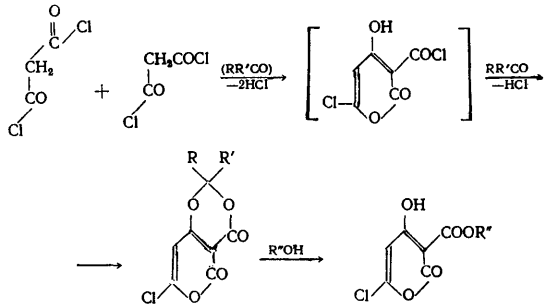
† For the structure of yangonin, see Chmielewska and coworkers.[77,78]

for obtaining the βδ-diketo-acids themselves (for example, under the action of acid anhydrides into acetonedicarboxylic acid[79-81]):

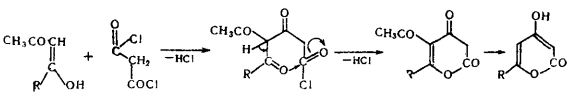


where R = CH_3, C_2H_5, C_3H_7.

Among the conversions of this type must be included the synthesis of 2-pyrones based on malonyl dichlorides‡ and its monoalkyl derivatives. Thus malonyl dichloride itself (in the presence of ketones, which act as weak bases) undergoes the following series of conversions[82]:



In the condensation of malonyl dichloride with acetylacetone, the pyronone isomeric with dehydracetic acid and containing an acetyl group at position 5 is formed[84]. The asymmetric β-diketone gives in these conversions the isomer corresponding to the preferential direction of the enolisation[84]:

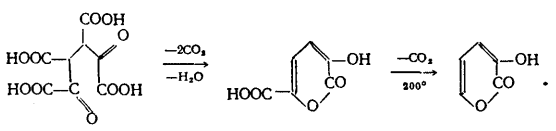


where R = CH_3, C_6H_5.

Esters of β-keto-acids (acetoacetic and benzoylacetic esters) behave similarly in reacting with malonyl dichlorides[85,86].

Hence the condensation of malonyl dichloride and its alkyl derivatives with β-dicarbonyl compounds — apparently proceeding through the stage of formation of acid chlorides corresponding to βδ-diketo-acids (type IV) — can serve as a general method of synthesis of 4-hydroxypyran-2-ones (pyran-2,4-diones).

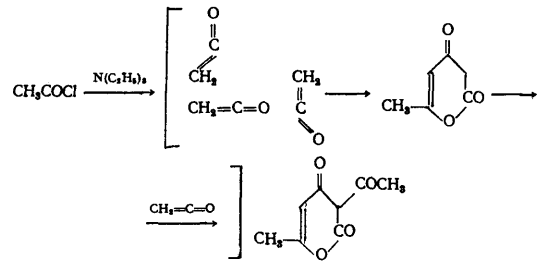
Unlike the βδ-diketo-acids, the αβ-diketo-acids (αα'-dioxalylsuccinic[87,88] and αβ-dioxalylpropionic[89] acids) are cyclised into derivatives of 3-hydroxypyran-2-one, for example:



‡ The condensation of malonyl dichloride in the presence of thiourea with the formation of compounds of the pyronone series has been described, but the precise structure of the products has not been established.[83]

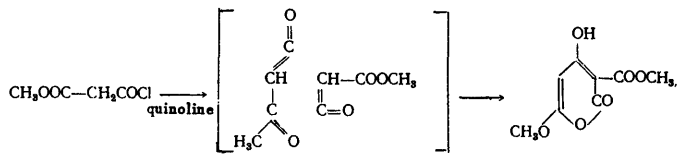
3. KETENS IN THE SYNTHESIS OF 2-PYRONES

2-Pyrones are formed by the action of tertiary amines on the halides of certain acids[90-92]. To explain the nature of the reactions it is assumed that initially ketens are formed, the cyclisation of which also leads to the formation of the corresponding 2-pyrones Thus the formation of dehydracetic acid from acetyl chloride is apparently the result of the trimerisation of keten into pyran-2,4-dione which is acylated further by another molecule of keten in the free 3-position[90]:

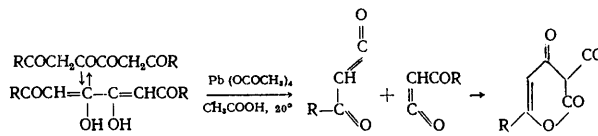


Under the same conditions propionyl chloride forms a homologue of pyran-2,4-dione (trimer of methylketen)[91].

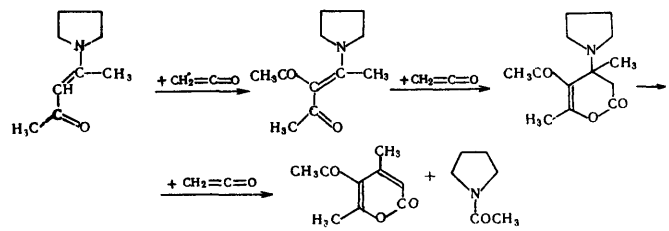
The conversion of methyl chloroformylacetate into a derivative of 2-pyrone evidently proceeds through the intermediate formation of the corresponding keten, which then dimerises[92]:



The action of lead tetra-acetate in acetic acid on 1,3,4,6-tetraketones gives compounds of the dehydracetic acid type; the process can be represented as the dimerisation of an acylketen formed as an intermediate in the splitting of the tetra-ketone[93]:

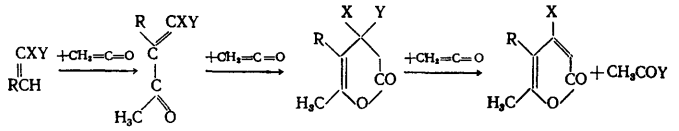


Another possibility of using keten in the synthesis of 2-pyrones consists in its reaction with enamines of carbonyl compounds. Thus, the reaction of the enamine of acetylacetone with keten evidently proceeds as follows[94]:



An ester of isodehydracetic acid is obtained analogously from the enamine of acetoacetic ester, and 1-methyl-3-oxocyclohexano[*c*]pyran from the enamine of cyclohexanone[94].

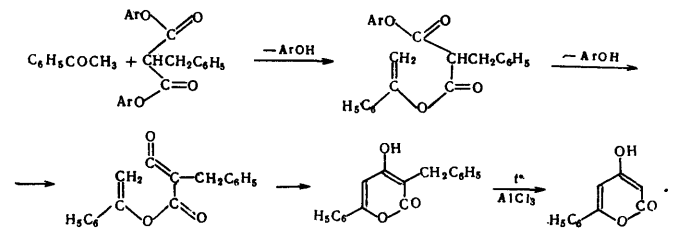
The reaction of keten and its homologues with *NN*- or *ON*-acetals of keten proceeds by the same scheme[95,96]:



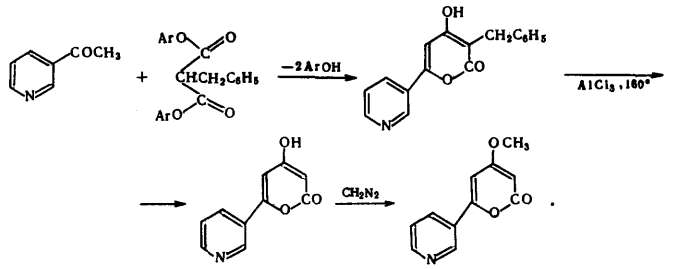
where X = NR'_2, Y = NR'_2, OAlk.

4. THERMAL CONDENSATION OF ESTERS OF SUBSTITUTED MALONIC ACIDS WITH KETONES

It was recently found that the thermal condensation of benzylmalonic esters with ketones which can be enolised can serve as a method for the synthesis of compounds of the 2-pyrone series§, for example[99]:



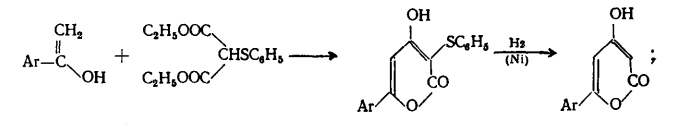
Use of various aliphatic–aromatic[99] and cyclic[100] ketones in this reaction gave (after debenzylation) 4-hydroxypyran-2-ones with a free 3-position[53]. On starting from 3-acetylpyridine, anibine (4-methoxy-6-pyrid-2-yl-pyran-2-one) was obtained by the same method in good yield[101]:



However, 4-methoxyparacotoin (see p. 176) could not be obtained in this way since the ammonium chloride used for debenzylation destroys the piperonyl residue[101].

It was subsequently shown that ethyl esters of malonic acids can be used successfully in this reaction instead of the less readily available diaryloic esters[102,103].

A variant of this method is the use of the diethyl phenylthiomalonate[104,105]:

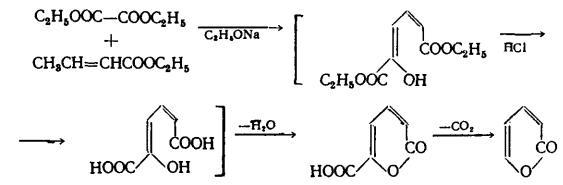


4-hydroxyparacotoin — Ar = 3′,4′-$(CH_2O_2)C_6H_3$ — was obtained in this way.

§ Thermal condensation of malonic esters with phenols is a well-known method of obtaining derivatives of 4-hydroxycoumarin.[97,98]

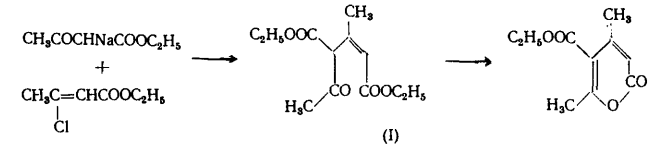
5. CYCLISATION OF αβ-UNSATURATED δ-KETO-ACIDS AND THEIR DERIVATIVES

An important method of synthesis of 2-pyrones is the cyclisation of unsaturated δ-keto-acids and their derivatives, which are often converted into pyrones even under the conditions of their production[106–109]; for example:



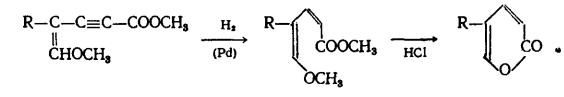
The linear homologues of crotonic ester (RCH_2–CH=$CHCO_2C_2H_5$) give 5-alkyl-2-oxopyran-6-carboxylic acid[110], the thermal decarboxylation of which leads to 5-alkylpyran-2-ones[110,111].

Anschütz and coworkers[112] synthesised ethyl isodehydracetate from the ester of the corresponding unsaturated keto-acid (I):

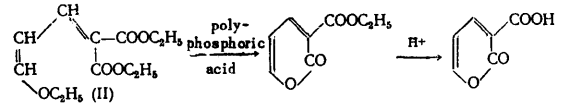


Sometimes αβ-unsaturated keto-acids or their derivatives are so easily cyclised into the corresponding 2-pyrones that their formation in any of these reactions can only be conjectured[113–116].

Attempts to obtain 2-pyrones by cyclisation of αβ-unsaturated δ-aldehydo-acids did not give positive results[110]; however, by using their enol esters for this purpose¶, Panizzi and Nicoletti[117,118] prepared 5-alkyl-substituted 2-pyrones (in poor yield)[117,118]:



In analogous fashion, diethyl 3-ethoxyallylidenemalonic acid (II) is cyclised into ethyl 2-oxopyran-3-carboxylate[119]:

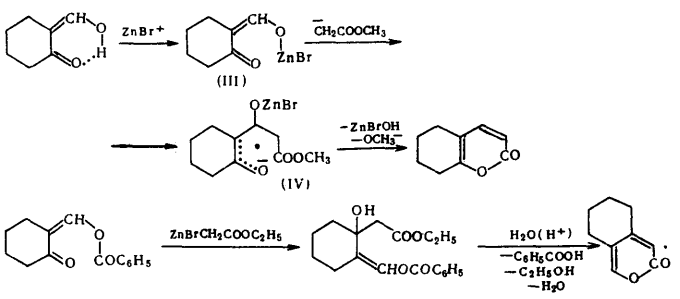


The cyclisation of the ester of the corresponding unsaturated keto-acid can also explain the formation of cyclohexano[*b*]pyran-2-one in the reaction of hydroxymethylenecyclohexanone and methyl bromoacetate (by the Reformatsky reaction).

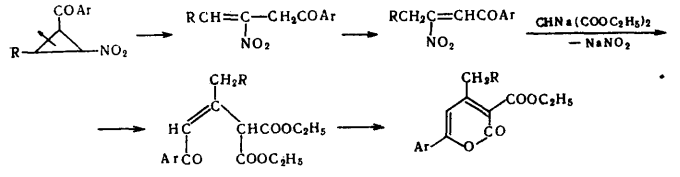
The salt of the enolate (III) gives the condensation product (IV) at the hydroxymethylene group so that only one of the two possible isomers is formed — cyclohexano[*b*]-pyran-2-one[120]. The other isomer, cyclohexano[*c*]pyran-3-one, is obtained on using 2-oxocyclohexylidenemethylbenzoate in this reaction, for which the formation of a salt

¶ Obtained by three-stage synthesis from methoxyacetonitrile.

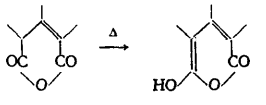
of type (III) is prevented and the reaction proceeds at the carbonyl group[121]:



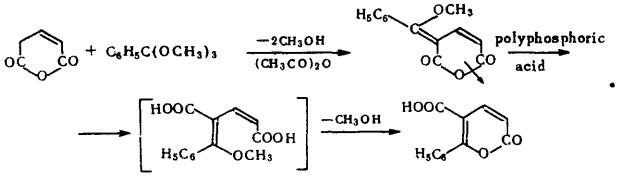
The intermediate formation of esters of $\alpha\beta$-unsaturated δ-keto-acids is also presumed in the production of 2-pyrones by condensation of 1-aroyl-2-nitrocyclopropanes† with bis-(ethoxycarbonyl)methylsodium[122-124]:



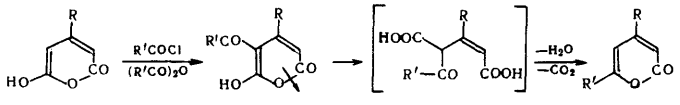
Several methods have recently been proposed for the preparation of 2-pyrones from anhydrides of glutaconic acids, which are characterised by an easy conversion into the isomeric 6-hydroxypyran-2-ones[125,126]:



These methods are also based on the cyclisation of the $\alpha\beta$-unsaturated δ-keto-acids and their derivatives which are formed as intermediates, for example[127]:

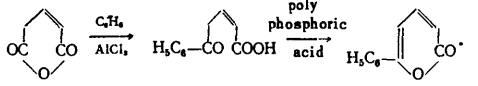


The action of acylating agents on β-methyl- and β-aryl--glutaconic anhydrides gives 5-acyl derivatives, from which it is easy to obtain 6-alkyl-4-methyl-[128-131], 6-alkyl--4-aryl-[132,133], and 4,6-diaryl-pyran-2-ones[134] (with ring opening and recyclisation with participation of the acyl group)[128]:



As a result of such conversions 3,5-diacylated glutaconic anhydrides give 3-acylpyran-2-ones[134].

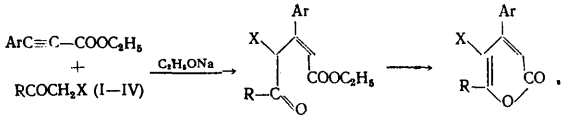
Another path for the use of anhydrides of glutaconic acids consists in their acylation of aromatic compounds; the unsaturated keto-acids thus formed are cyclised further into 6-arylpyran-2-ones, for example[127]:



This method was used with β-substituted glutaconic anhydrides to give a series of 4,6-diarylpyran-2-ones[135-137] and 6-aryl-2-oxopyran-4-carboxylic acids[138].

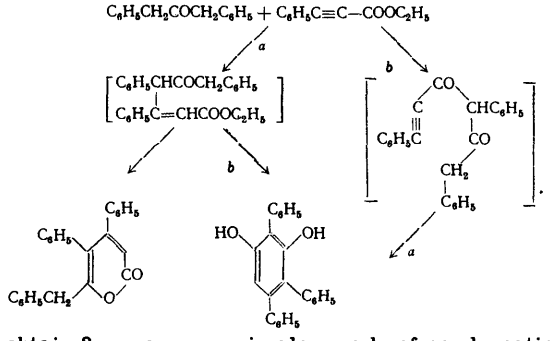
6. CONDENSATION OF $\alpha\beta$-ACETYLENE ACIDS AND KETONES WITH COMPOUNDS CONTAINING AN ACTIVE METHYLENE GROUP

The condensation of esters of propiolic acids with compounds having an active methylene group — benzyl ketones (I)‡[142-144], ω-alkoxy and ω-aryloxyacetophenones (II)[145], esters of β-keto-acids (III)[146-148], β-diketones (IV)[149] — is widely employed for the synthesis of 2-pyrones; their formation is the result of the dehydration of the $\alpha\beta$-unsaturated δ-keto-acids which are formed as intermediates:

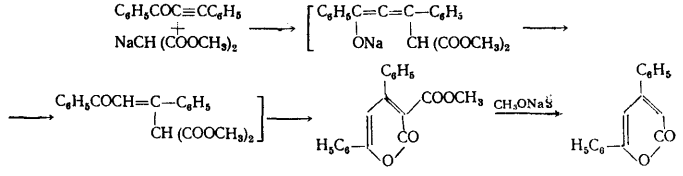


(I) X = C_6H_5; (II) R = Ar, X = OR'; (III) X = $COOC_2H_5$; (IV) X = COR'

Ketones with two active methylene groups form, in addition to the corresponding 2-pyrones, derivatives of resorcinol, the formation of which is explained by the successive occurrence of Michael (*a*) and Claisen (*b*) condensations[150]:



To obtain 2-pyrones use is also made of condensation of ketones of the acetylene series with compounds containing a labile hydrogen atom[151-154], for example[151]:



When the second component in this reaction is methyl α-cyanopropionate, 3-methyl-4,6-diphenylpyran-2-one[156] is obtained.

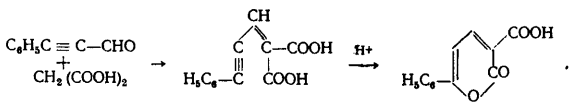
† Under these conditions the corresponding acylnitrocyclopropanes give not only the corresponding 2-pyrones but also appreciable quantities of resorcinol derivatives.[124]

‡ With aliphatic, aliphatic–aromatic, and cyclic ketones the condensation takes place with the formation of derivatives of 4--pyrone.[139-141]

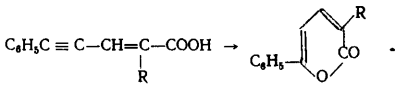
§ It was later shown that the product of the reaction of either 3--carbethoxycarbonyl-6-methyl-4-phenylpyran-2-one[153] or 5-acetyl--6-methyl-4-phenylpyran-2-one[148] with sodium ethoxide is not, however, 6-methyl-4-phenylpyran-2-one.[155]

7. CYCLISATION OF ALKEN-2-YN-4-OIC ACIDS

2-Pyrones can be obtained by the cyclisation of dibasic enynoic acids [109,157] (formed in the condensation of aldehydes of the acetylene series with malonic acid [158-161]) under the action of acidic reagents, for example [109]:

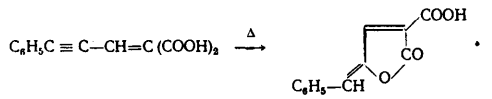


Monobasic enynoic acids are also cyclised in acid media [161-166] or on heating in the presence of mercury sulphate [160], into the corresponding 2-pyrones:

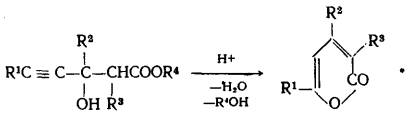


where R = H, or Ar.

However, both types of these acids can also be cyclised (on heating) in another direction — with formation of five-membered unsaturated lactones (derivatives of protoanemonin) [109,162,165], for example:



The cyclisation of enynoic acids forms the basis of a recently proposed method for the production of 4,6- and 3,4,6-substituted 2-pyrones from esters of 3-hydroxy-alkyn-4-oic acids [155]:

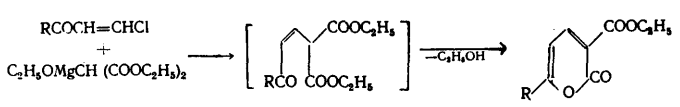


8. 2-CHLOROVINYL KETONES IN THE SYNTHESIS OF 2-PYRONES

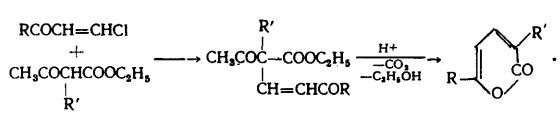
Kochetkov and coworkers used 2-chlorovinyl ketones for making 2-pyrones; these ketones have been widely used in the preparation of other heterocyclic compounds [167].

The reaction of 2-chlorovinyl ketones with substances having a labile α-hydrogen atom leads to the formation of $\beta\gamma$-unsaturated δ-keto-acids, which are readily cyclised into the corresponding 2-pyrones.

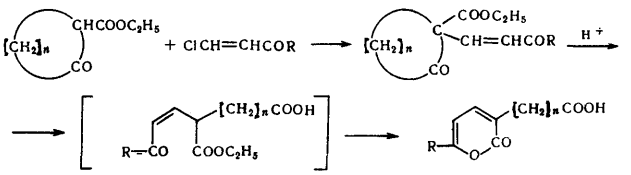
The use in this reaction with 2-chlorovinyl ketones of bis(ethoxycarbonyl)methylmagnesium ethoxide [168,169]:



mono-substituted acetoacetic esters [170,171]:

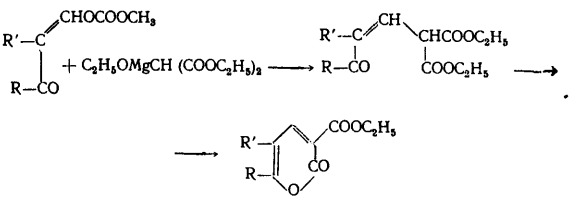


and also esters of cyclic β-keto-acids [170,172]:



can serve for the preparation of 3,5-disubstituted 2-pyrones.

Analogues of 2-chlorovinyl ketones have been used in this reaction: 2-alkoxyvinyl ketones [173] and *O*-alkoxycarbonyl derivatives of the enol forms of β-dicarbonyl compounds [174]; for example:

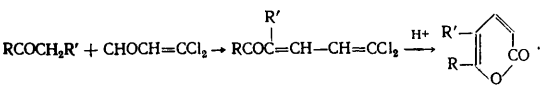


9. $\alpha\beta$-UNSATURATED $\beta\beta$-DICHLOROALDEHYDES AND $\beta\beta$-DICHLOROKETONES IN THE SYNTHESIS OF 2-PYRONES

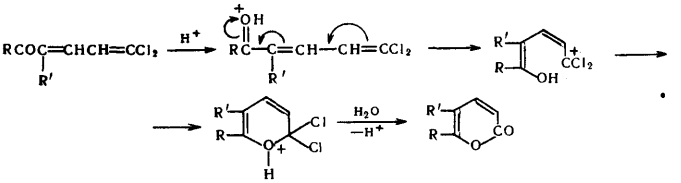
2,2-Dichloroacryladelhyde, which is readily obtainable from the telomer of carbon tetrachloride and vinyl ethers [175,176]:

$$CCl_4 + CH_2{=}CHOR \rightarrow CCl_3CH_2CHClOR \xrightarrow{-HCl} CCl_2{=}CH{-}CHClOR \xrightarrow{-RCl} CCl_2{=}CHCHO,$$

was the basis of Zakharkin and coworkers' development of a new synthesis of 2-pyrones, the first stage of which is the condensation of dichloroacrolein with alkyl aryl ketones (R = Alk, R′ = Ar) [163,164,177-179] with acetoacetic ester (R = CH_3, R′ = $CO_2C_2H_5$) [177-179], pyruvic acid (R = = CO_2H, R′ = H) [180] under the action of hydrogen chloride [177], metallic sodium [163], or barium hydroxide [164,178]:



The authors put forward the following mechanism for the cyclisation of the 3,3-dichloroallyl diketones which are formed as intermediate [177]:



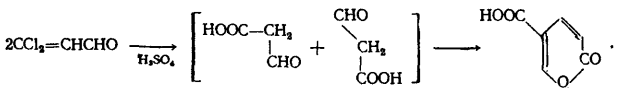
The chloroacetal $CCl_2{=}CH{-}CHClOR$ or the telomer $CCl_3CH_2CHClOR$ [181], formed as an intermediate in the preparation of 2,2-dichloroacrylaldehyde, can be used in this reaction instead of the latter.

The use of 2,2-dichloro-1-methylacrylaldehyde allows derivatives of 2-pyrone with a methyl group in position 3 to be obtained [179].

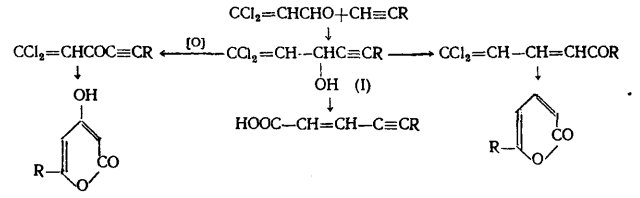
Cyclic β-diketones react with 2,2-dichloroacrylaldehyde [182] or trichloroacrylaldehyde [183,184] to form the corres-

ponding 2-pyrones (without isolation of the intermediate condensation products).

The intermolecular condensation of 2,2-dichloroacrylaldehyde leads to coumalic acid (apparently through the stage of the formation of formylacetic acid)[180]:

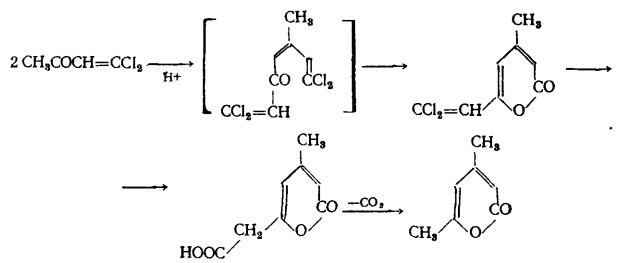


2,2-Dichloroacrylaldehyde was used to make 2-pyrones in another way. On its reaction with the metal derivatives of monosubstituted acetylenes, methanol derivatives (I) were obtained, which were subsequently converted into 2-pyrone derivatives[163,164,178,186]:



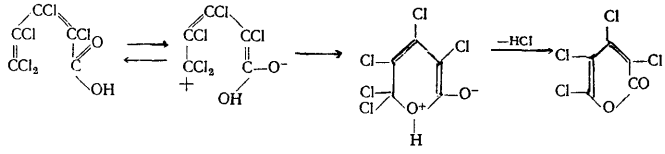
This method was used to prepare paracotoin (6-piperonylpyran-2-one)[164,178] and 3-methyl-6-phenylpyran-2-one[164].

2-Pyrones were also obtained by using 2,2-dichlorovinyl ketones, whose intermolecular condensation takes place by the scheme given above for 2,2-dichloroacrylaldehyde[185]:



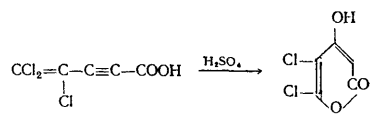
10. CYCLISATION OF POLYCHLORODIENOIC ACIDS

Roedig and Märkl[187] showed that polychlorodienoic acids are cyclised into polychloropyran-2-ones¶ on heating to 180–200°[187,188] or on heating their acid chlorides with concentrated sulphuric acid to 50°:[189]



ω-Bromoperchloropenta-2,4-dienoic acid[187] and perchloropenta-2,4-dienoic acid[190] behave similarly.

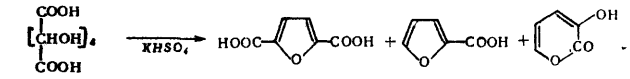
It is interesting to note that trichlorovinylpropiolic acid is converted into 5,6-dichloro-4-hydroxypyran-2-one on standing with concentrated sulphuric acid[191]:



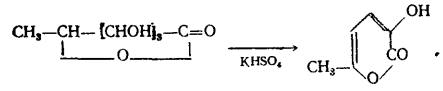
¶ The chlorine atoms in positions 4 and 6 of 2-pyrones are readily replaced by hydrogen on reduction with zinc and acetic acid.[187,190]

11. POLYHYDROXY-COMPOUNDS IN THE SYNTHESIS OF 2-PYRONES

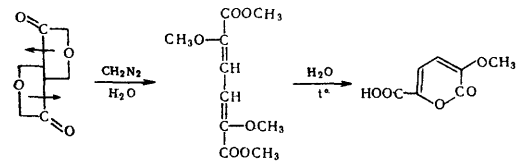
In the dry distillation of mucic acid, in addition to pyromucic (and dehydromucic) acid, an acid isomeric with it is formed, termed isopyromucic acid[192], which, as Chavanne showed[193–198], is 3-hydroxypyran-2-one. A better yield of isopyromucic acid is obtained on heating mucic acid with potassium hydrogen sulphate[198–200] (isopyromucic acid can be separated from pyromucic and dehydromucic acids by making use of their different acidities[201]:



Similarly, 3-hydroxy-6-methylpyran-2-one is formed in the distillation of rhamnolactone[202–204]:



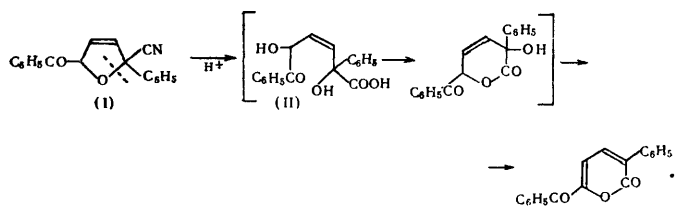
The action of moist diazomethane on the dilactone of mannosaccharic acid gives methyl 2,5-dimethoxymuconate, which is converted on boiling with water into 3-methoxy-2-oxopyran-6-carboxylic acid[105]:



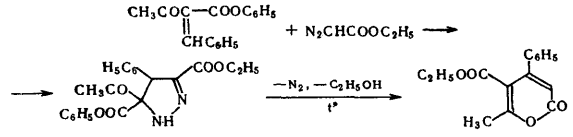
3-Hydroxypyran-2-one and its derivatives are also formed on distilling other polyhydroxy-compounds[198,206].

12. FIVE-MEMBERED HETEROCYCLIC COMPOUNDS IN THE SYNTHESIS OF 2-PYRONES

The conversion of some compounds of the 2,5-dihydrofuran and pyrazoline series into derivatives of 2-pyrones has been described. Thus, in the hydrolysis of substituted 2,5-dihydrofuran (I) the corresponding 2-pyrone is formed — through the intermediate stages of opening of the furan ring with subsequent cyclisation and dehydration of the dihydroxyketo-acid (II) which is formed[207]:

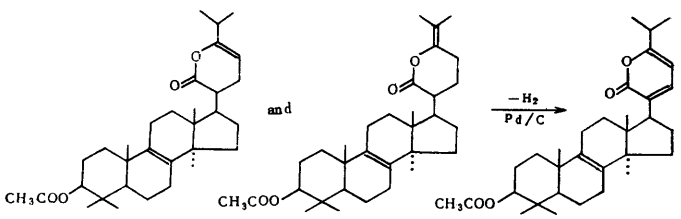


Another example of such a reaction is also well known[208]. The conversion of substituted pyrazolines into the corresponding 2-pyrones has been described[209,210], for example:



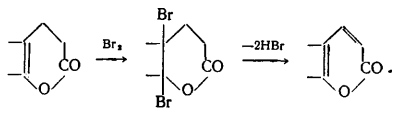
13. δ-LACTONES IN THE SYNTHESIS OF 2-PYRONES

Recently the catalytic dehydrogenation of triterpenoidal δ-enol-lactones into the corresponding 2-pyrones was described[211,212]:



This exhausts the literature on the direct dehydration of δ-lactones.

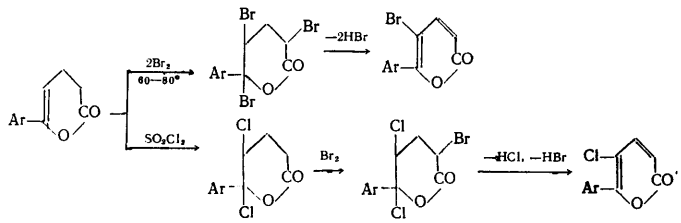
In recent years the indirect dehydration of δ-enol-lactones into 2-pyrones has been developed extensively. Shusherina and coworkers have carried out the conversion of δ-enol-lactones into 2-pyrones by brominating the former and then dehydrobrominating the dibromides which are formed (during their distillation)[213,214]:



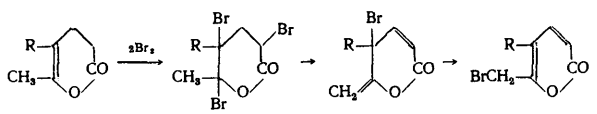
The reaction can serve as a preparative method for obtaining cycloalkano[*b*]- and 5,6-dialkyl- (or 5,6-alkylaryl-) -pyran-2-ones[213,215,216].

The chlorination of δ-enol-lactones (by the action of sulphuryl chloride) with the subsequent dehydrochlorination of the dichlorides was used for the same purpose[217,218].

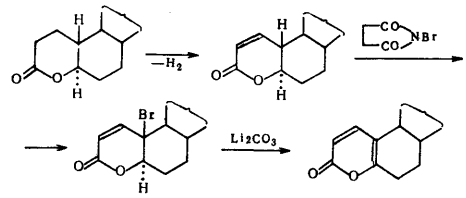
The halogenation of 6-aryl-3,4-dihydropyran-2-ones at the double bond and at the α-methylene group and subsequent dehydrohalogenation is a preparative method for the synthesis of 6-aryl-5-halogenopyran-2-ones[219,220]:



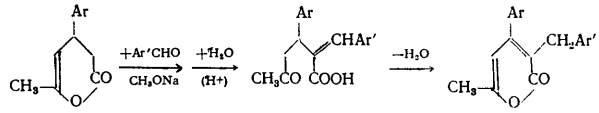
The same series of conversions for 5-alkyl- or 5-aryl- -3,4-dihydro-6-methylpyran-2-ones leads to the production of monohalides of another type — 6-bromomethylpyran- -2-ones, the formation of which is apparently the result of a rearrangement of the intermediate, allyl bromide[221]:



Recently, by the example of steroidal compounds, a method was developed for making 2-pyrones from saturated δ-lactones by partial dehydrogenation in positions 3 and 4 of the lactone ring and subsequent bromination in the allyl position followed by dehydrobromination of the monobromide formed[222]:



What is in principle another method of converting 3,4-dihydropyran-2-ones with an aryl group in position 4† into 2-pyrones has been described — their condensation with aromatic aldehydes and subsequent cyclisation (with isopropenyl acetate) of the α-benzylidene-δ-keto-acids which are formed[223]:



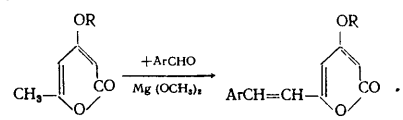
14. PRODUCTION OF 2-PYRONES FROM COMPOUNDS WHICH ALREADY CONTAIN THE PYRONE RING

Reactions of 2-pyrones which take place with retention of the pyrone ring can be used for converting one type of 2-pyrone into another and serve for the production of pyrones of a given structure.

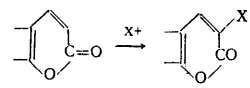
Thus, decarboxylations (see above) are widely used for going from oxopyrancarboxylic acids to 2-pyrones devoid of functional substituents[19,39]. For example, 6-phenylpyran-2-one can be obtained by decarboxylation of all the isomeric 2-oxo-6-phenylpyrancarboxylic acids[115,127,138,160]. The reduction of certain 2-pyrone derivatives is also used for this purpose — 4-chloropyran-2-ones[48], 3-chloromethylpyran-2-ones[224], 5-bromopyran-2-ones[218,219], and 6-bromomethylpyran-2-ones[221].

Homologues of 2-pyranones can be obtained by methylating the pyrone ring with methyl iodide in the presence of potassium hydroxide[225] or with diazomethane[226,227].

The alkyl groups of certain derivatives of 2-pyrone exhibit the ability to undergo condensation with aromatic aldehydes[86,228]. Thus the condensation of esters of 4-hydroxy-6-methylpyran-2-one with corresponding aldehydes gives yangonin[59] and hispidin[229]:



An electrophilic substitution of 2-pyrones recently completed allows derivatives of 2-pyrones with a functional substituent in the 3-position to be obtained[230-235]:



where X = NO_2, SO_3H, SO_2Cl, CH_2Cl.

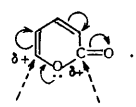
† When there is not an aryl group in position 4, then unsaturated lactones with one double bond in the ring and the other in the exocyclic position are formed.

III. CHEMICAL PROPERTIES OF 2-PYRONES

2-Pyrones exhibit an unusual combination of properties, of which the best known is their ability as unsaturated lactones to react with various nucleophilic reagents. The ability of 2-pyrones to enter into diene synthesis has been much less studied. The electrophilic substitutions of 2-pyrones which characterise these heterocyclic systems as aromatic have been investigated only recently.

1. REACTION OF 2-PYRONES WITH NUCLEOPHILIC REAGENTS

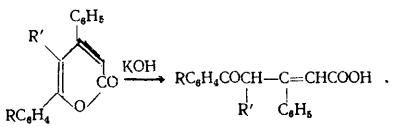
Nucleophilic reagents whose action on 2-pyrones is accompanied by ring opening attack the pyrone ring in position 2 or 6‡, which agrees with the representation of the electron density distribution in the α-pyrone ring:



In which of these directions any particular reagent will react is apparently determined mainly by the thermodynamic stability of the addition products which are formed[236].

Hydrolysis

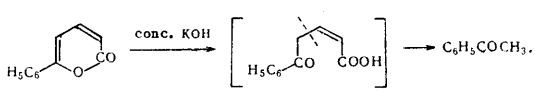
Under the action of aqueous or alcoholic solutions of alkalis the pyrone ring is broken and unsaturated δ-keto-acids are formed[68,72,73,120,135,137,144,145,242,243§]; for example[145]:



The production of unsaturated δ-keto-acids as hydrolysis products can be considered as the result of the addition of water to the α-pyrone ring at the 1,2- or 1,6-bonds.

In individual instances the unsaturated keto-acids are very easily cyclised (on acidifying the salts) into the original 2-pyrones[225].

Hydrolysis of 2-pyrones with concentrated alkali is frequently accompanied by subsequent hydrolytic splitting¶ of unsaturated keto-acids[20,26,39,68,142,243,247]; for example[246]:

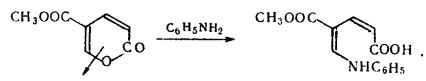


Examples are known of great stability in the α-pyrone ring under hydrolysis conditions. Thus, 3,5-di-t-butylpyran-2-one could be hydrolysed only by prolonged heating with alkali at 150° (in glycerol solution)[243].

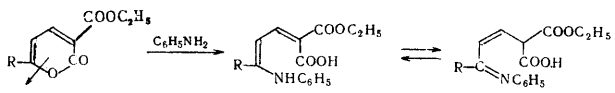
Reaction with Ammonia and Amines

Unlike hydrolysis, the addition of ammonia or amines to 2-pyrones can lead to different reaction products, depending on whether the 1,2- or the 1,6-bond of the α-pyrone ring is broken.

Pechmann and Welsh[248] showed that in the reaction of methyl coumalate with aniline δ-anilino-γ-methoxycarbonylsorbic acid is formed, that is, primary amines are attached at the 1,6-bond of the α-pyrone ring:

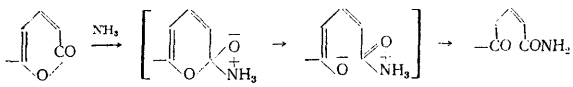


Such a presentation of the way 2-pyrones react with ammonia and primary amines is also confirmed by the results of Kochetkov and Kudryashov[249], who obtained 2-ethoxycarbonyl-5-phenyliminoalkadienecarboxylic acids by the reaction of 6-alkyl-3-ethoxycarbonylpyran-2-ones with aniline:



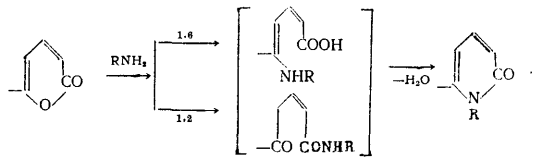
where R = CH_3, C_3H_7, C_5H_{11}.

A second possible direction of the reaction of 2-pyrones with ammonia and amines has also been discussed in the literature[187,251,252]; it is accompanied by breaking of the 1,2-bond of the α-pyrone ring and leads to the production of amides of unsaturated δ-keto-acids; it is suggested that the reaction starts here with attack of the carbonyl group of the 2-pyrone[251]:



However, such a course of the reaction has not been confirmed.

Usually the action of ammonia and primary amines on 2-pyrones gives 2-pyridones, the formation of which can be considered, in the light of the above data, to be the result of the dehydration of addition products which are formed initially:



The conversion of 2-pyrones into pyridones under the action of ammonia occurs both in the cold[35,123,124,151,187,247,248,253-255], and on heating[112,113,144,145,256,257]; instead of ammonia, ammonium acetate is sometimes used[107,110,189,258-260,266].

The production of *N*-substituted pyridones[187,248,250,256,259,261-265,267] by the action of primary amines on 2-pyrones (in the cold or on heating) is often used for confirming the structure of 2-pyrones.

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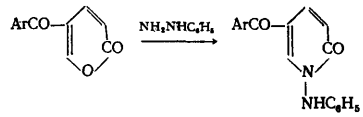
‡ Saturated and unsaturated γ and δ lactones also react with nucleophilic reagents along these two directions[237,238] but usually under milder conditions than for pyrones.[239-241]

§ The action of alkali metal alkoxides on 2-pyrones leads to the formation of esters of unsaturated δ-keto-acids.[126,151,246]

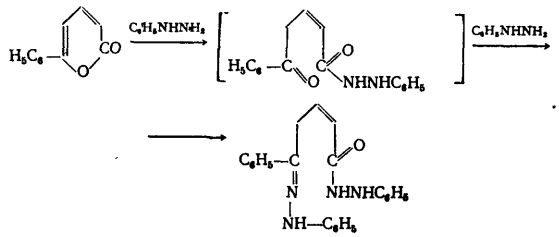
¶ Therefore the hydrolysis of 2-pyrones is not used for their identification in distinction from the hydrolysis of δ-enol-lactones, (3,4-dihydropyran-2-ones).[244,245]

The reaction of 2-pyrones with phenylhydrazine leads either to *N*-substituted pyridones or to the amides of δ-keto--acids.

Thus, 5-aroylpyran-2-ones readily react with phenylhydrazine to give the corresponding *N*-aminopyridones[256]:



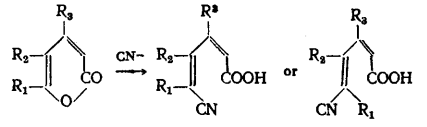
where Ar = C_6H_5, *p*-$CH_3C_6H_4$, *p*-ClC_6H_4, *p*-BrC_6H_4, whereas 6-phenylpyran-2-one forms the phenylhydrazide of the corresponding unsaturated δ-acid (isolated as the phenylhydrazone)[225]:



The reaction of 2-pyrones with hydrazine, hydroxylamine, and semicarbazide leads to the formation of *N*-substituted pyridones[144,145,257,268]†.

Reaction with Sodium Cyanide

Recently Vogel[270] carried out a new reaction of opening the α-pyrone ring at the 1,6-bond under the action of the cyanide ion, which leads to the formation of mononitriles of unsaturated acids of the muconic acid type:



The stereochemical directionality of this astonishingly easy reaction (it ends after 5–10 min in the cold) can be controlled by choice of solvent.

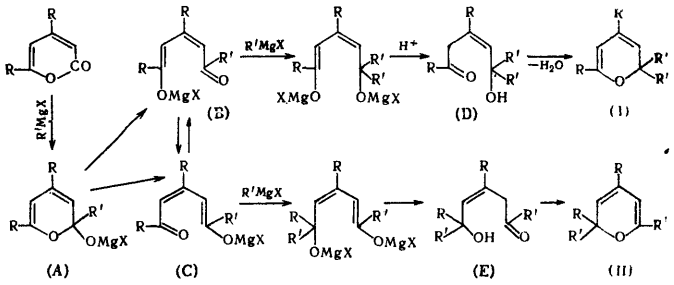
Reaction with Grignard Reagents

The reaction of pyrones with organomagnesium compounds is quite complicated. Gompper and Christmann[271], who first studied this reaction, ascribed to the compounds obtained the structure of pyrans (I):



(I)

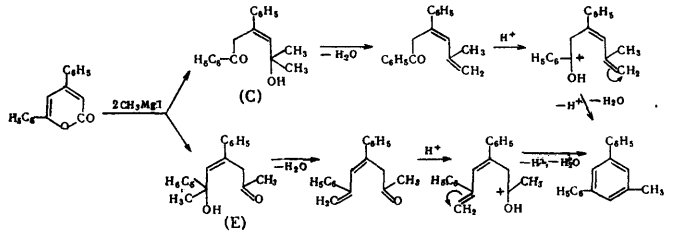
It was shown later[272] that pyrans of structure (II) can also be formed which is explained[273] by the existence of an equilibrium between the two forms of enolates, (B) and (C), which are formed from the initial addition product (A):



(A) (B) (C) (D) (E) (I) (II)

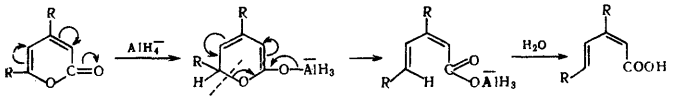
When the pyrone is taken in excess at R or R′ = Ar then aromatic hydrocarbons are formed in 60–80% yield[95,274].

Apparently, the keto-alcohols (D) and (E) are dehydrated initially into doubly-unsaturated ketones, which are cyclised subsequently by a Prins type of intramolecular reaction[275], for example:



Reduction by Hydro-Complexes of Metals

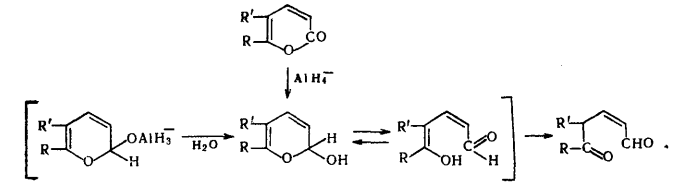
Hydro-complexes of metals react with 2-pyrones to reduce these to unsaturated acids[276–278] (or under more severe conditions — to unsaturated alcohols[211,212,277,278]), the formation of which is explained, apparently, by the addition of an aluminium hydride anion at the carbonyl group of the 2-pyrone and the hydride ion at position 6 and by subsequent opening of the ring at the 1,6-bond:



Hence the final result of this conversion is the hydrogenolysis of the 1,6-bond of the α-pyrone ring‡.

† Wiley and coworkers[269] showed that the action of hydrazine on ethyl isodehydracetate takes place anomalously with the formation of 3-methylpyrazol-5-one.

‡ However, in other instances during the reduction of 2-pyrones by lithium tetrahydroaluminate hydrogenolysis of the 1,2-bond of the α-pyrone ring takes place with formation of unsaturated δ-keto--aldehydes[279] or of the products of their further reduction — unsaturated 1,5-diols[280,281]; for example[279]:



The ease of reduction depends both on the structure of the initial 2-pyrone and on the activity of the metal hydro-complex used. Thus, coumalic acids are reduced at even 0–10° by such mild agents as sodium or lithium tetrahydroborate [277,278].

Sodium or lithium tetrahydroborate very readily reduces 4-methoxy-6-methylpyran-2-one, being converted into the corresponding unsaturated acid; the action of lithium tetrahydroaluminate forms a further reduction product — an unsaturated alcohol [278]. 4,6-Dimethylpyran-2-one is reduced to an unsaturated acid only by lithium tetrahydroaluminate [277,278].

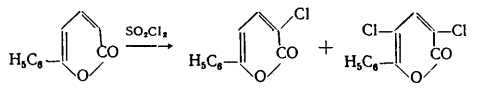
2. ELECTROPHILIC SUBSTITUTIONS IN THE 2-PYRONE SERIES

In accordance with the polarisation of the bonds of the α-pyrone ring it must be expected that the attack of electrophilic reagents will be directed to the third or fifth carbon atom of the ring.

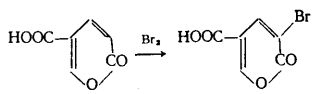
(a) Halogenation

Chlorination. The action of chlorine on coumalic [254] and isodehydracetic [26] acids gave the corresponding monochloro-substituted acids. The position of the chlorine atom was shown by the conversion of one of them (chlorocoumalic acid) into the known 3-chloropyridine [254].

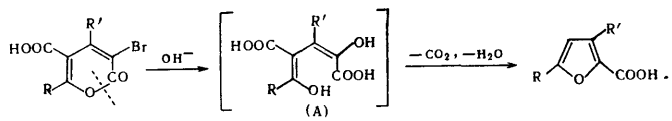
It was recently shown that the chlorination of 2-pyrones takes place very readily under the action of sulphuryl chloride [282]. Thus, under its action 6-phenylpyran-2-one is converted even in the cold into a mixture of mono- and di-chloro-derivatives:



Bromination. Bromination is one of the most studied substitutions of 2-pyrones. Under the action of bromine replacement of one or two (depending on the reaction conditions and the structure of the initial pyrone) hydrogens of the α-pyrone ring takes place. Thus, during the bromination of isodehydracetic [23,26,31,33] and coumalic [28,248,256,253] acids and their esters the corresponding monobromo-derivatives were obtained, for example [248]:

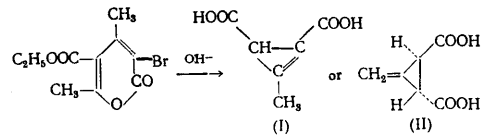


To prove the position of the bromine atom, Feist [26,283,284] used the alkaline hydrolysis of these bromo-substituted 2-pyrones; the hydroxy-acids which are formed as intermediates in the opening of the pyrone ring are cyclised into the corresponding α-furancarboxylic acids, the formation of which is possible only when the bromine atom in the initial bromopyrones is in position 3:



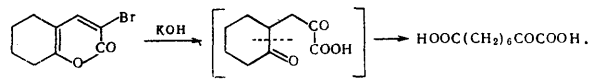
Conversion into α-furancarboxylic acids was used to establish the structure of the bromination products of other 2-pyrones [37,209,247,285–287]. However, examples have been described of the anomalous behaviour of bromopyrones under the action of alkalis.

Thus, in the alkaline hydrolysis of the ethyl ester of brominated isodehydracetic acid [112] a substance was isolated [26,284] which is best known in the literature as Feist's acid, for which two structures were proposed later — 2-methylcyclopropene-1,3-dicarboxylic acid (I) [27] and *trans*-3-methylenecyclopropane-1,2-dicarboxylic acid (II) [288]:



Bottini and Roberts [292] supported structure (II) on the basis of a study of NMR spectra.

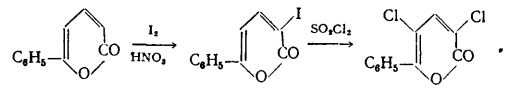
Another example, which illustrates the anomalous behaviour of bromopyrones in reacting with alkali is the formation of α-ketoazelaic acid from 3-bromo-5,6,7,8-tetrahydrochromen-2-one [289]:



In the bromination of 2-pyrones in which positions 3 and 5 are free, the bromine enters the 3 position in the cold [37,128,129,185,191] and on heating into the positions 3 and 5 with the formation of dibromopyran-2-ones [290,291].

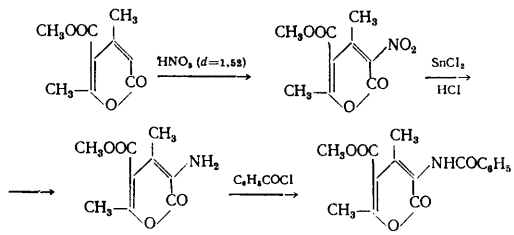
Hardly anything has been published on the reactivity of bromopyran-2-ones. Pechmann [254] described an unsuccessful attempt to replace the bromine atom in bromopyrones by the action of various nucleophilic reagents, showing at the same time the exceptional inertness in these reactions of the bromine connected to the α-pyrone ring.

Iodination. It was recently shown, by the example of 6-phenylpyran-2-one, that under conditions of oxidative iodination (118°, in the presence of concentrated nitric acid) iodine enters the pyrone ring to form 3-iodo-6-phenylpyran-2-one, the structure of which was confirmed by conversion into the well-known 3,5-dichloro-compound§ [282]:



(b) Nitration

The nitration of 2-pyrones was first carried out by Angeli [293], by the example of methyl isodehydracetate; the structure of the reaction product was shown much later [294] by the reduction of the nitro-group and the subsequent benzoylation of the amine formed:

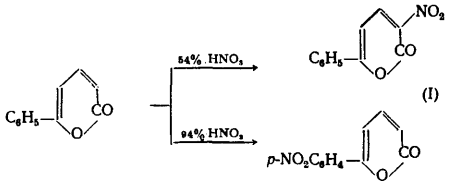


§ The iodination of 3-hydroxypyrone by iodine in the presence of yellow mercury oxide has been described [198], but the structure of the monoiodopyran-2-one thus obtained has not been established.

In other studies it was assumed, by analogy with brominations, that the nitro-group enters the 3-position [33,231,295].

Ciamician and Silber [225] obtained 3-nitro-6-phenylpyran-2-one on nitrating 6-phenylpyran-2-one with 70% nitric acid¶; its structure was recently shown by Zakharkin and Sorokina [246] who converted it into α-amino-δ-phenylvaleric acid. On the basis of this the authors [246] drew the general conclusion that the nitration of 6-phenylpyran-2-one by nitric acid takes place only in the pyrone ring.

However, Shusherina and coworkers [296] showed that by varying the nitric acid concentration 6-phenylpyran-2-one can be selectively nitrated. Thus, when 94% nitric acid is used the nitro-group only enters the benzene ring but with 54% nitric acid only in the pyrone ring:



(I)

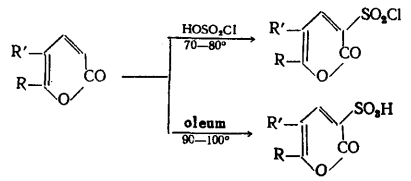
(II)

This feature of the behaviour of 6-phenylpyran-2-one is evidently explained by the greater stability of the oxonium complex in more concentrated acid, which should lead to a decrease in the reactivity of the α-pyrone ring as regards the electrophilic substitutions [296].

In the nitration of 6-phenylpyran-2-one [290] and isomeric methylphenylpyran-2-ones [231] with nitrating mixture, the nitro-group enters only the benzene ring.

(c) Sulphochlorination and Sulphonation

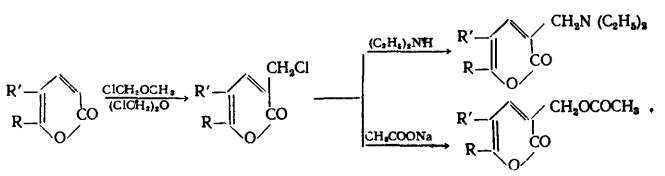
Shusherina and coworkers first effected the sulphochlorination [232] (yield 30–50%) and sulphonation [233] (yield ~ 50%) of 5,6-disubstituted pyran-2-ones:



where R = R′ = CH_3; or R = CH_3, R′ = C_3H_7, C_4H_9.

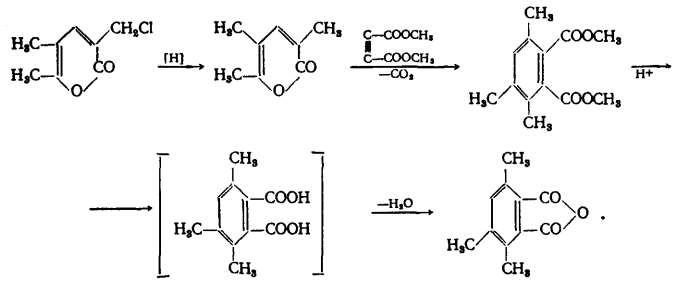
(d) Chloromethylation

2-Pyrones are chloromethylated in position 3 under the action of a mixture of mono- and bis-chloromethyl esters or of formalin saturated with hydrogen chloride. The chloromethylpyran-2-ones obtained (yield 35–41%) readily undergo exchange reactions [234,235]:



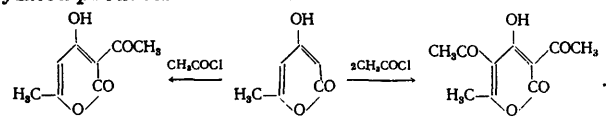
¶ The authors of the present article have shown that in addition to 3-nitro-6-phenylpyran-2-one under these condicitions 6-*p*-nitro-phenylpyran-2-one is also formed (ratio 8 : 1). [290]

The position of the chloromethyl group was shown by converting 3-chloromethyl-5,6-dimethylpyran-2-one into a homologue of phthalic anhydride with a known position of the substituent [224]:



(e) Acylation

As yet the Friedel-Crafts reaction has been accomplished only for hydroxypyran-2-ones. Thus in the acylation of 4-hydroxy-6-methylpyran-2-one acyl chlorides of carboxylic acids form a mixture of the mono- and di-acylated products [54,85,291,298]:



4-Hydroxy-6-methylpyran-2-one is an example of a compound which has been formylated [297] by a mixture of carbon monoxide and hydrogen chloride in the presence of trifluoroacetic acid, but the structure of the products of the reaction has not been shown.

From the reactions considered in this section it has long been known that for pyrones halogenation and nitration are not typical of an electrophilic substitution, since they can proceed either by an ionic or by a radical mechanism. Possibly this is why 2-pyrones were not considered to be aromatic systems until recently.

The suggestion that 2-pyrones were of aromatic character was made recently by Mayer [300], who drew this conclusion on the basis that 2-pyrone is an isoelectronic analogue of tropone:



Such typical electrophilic substitutions as sulphuration, sulphochlorination [232], chloromethylation [235], and nitration with nitrating mixture [231] which have been performed for pyrones confirm Mayer's hypothesis and allow this class of heterocyclic compounds to be placed among non-benzenoid aromatic systems.

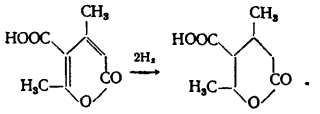
The conclusion about the aromatic nature of 2-pyrones and also about the similarity of 2-pyrones with tropones was confirmed recently [301,302] by Sheinker and coworkers from a study of the intensity of the absorption bands of the carbonyl group in the infrared spectra of 2-pyrones.

3. REACTION OF ADDITION AT THE DOUBLE BONDS OF THE α-PYRONE RING

A characteristic of the 2-pyrones is reactions which involve compounds with a system of conjugated double bonds — catalytic hydrogenation and diene synthesis.

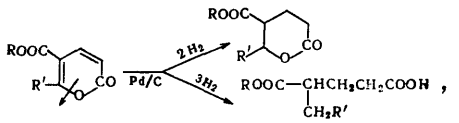
(a) Catalytic Hydrogenation

2-Pyrones easily add on hydrogen at the double bonds to form lactones — tetrahydropyran-2-ones, for example[303]:



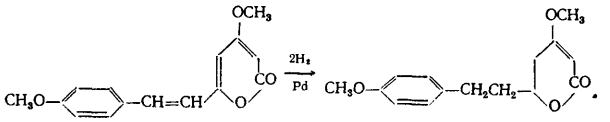
Hydrogenation catalysts which have been used for 2-pyrones are: palladium on carbon[129,303], barium sulphate[170,304], and also palladium black[305].

In addition to the addition of hydrogen at the multiple bonds of the α-pyrone ring, under catalytic hydrogenation conditions hydrogenolysis of the 1,6-bond is observed, leading to the formation of acids[226,303] (sometimes as the main product of the reaction):



where R = R′ = H and CH_3.

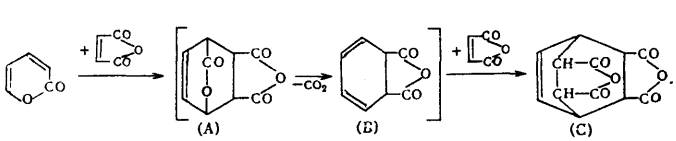
Selective hydrogenation (in the 5,6 position) of the α-pyrone ring has been achieved under certain conditions[305-307]. Thus yangonin gave 5,6-dihydro-4-methoxy--6-(*p*-methoxyphenethyl)pyran-2-one, the narcotic action of which is connected specifically with the absence of a double bond in the 5,6 position of the α-pyrone ring[307]:



Catalytic hydrogenation was used to prove the structure of certain natural compounds containing an α-pyrone ring — scillaren A[8], cinobufagine[6], bufotalinin, and marinobufagin[308].

(b) Diene Synthesis

A distinctive property of 2-pyrones is their ability to undergo the diene synthesis. On studying the reaction of 2-pyrone and methyl coumalate with maleic anhydride, Diels and Alder[309] showed that a mono-addition product (A)† is formed at 110°, which is decarboxylated at 130–140° into the 1,2-dihydrophthalic anhydride (B); the latter reacts with another molecule of maleic anhydride, forming a bridging addition product (C):



(A) (B) (C)

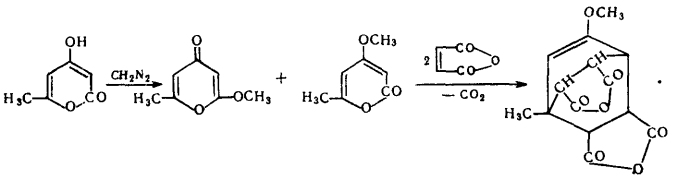
It was subsequently found that apart from the temperature the essential factor determining the course of the reaction is the structure of the 2-pyrone. Thus 5-alkylpyran-2-ones[110,117] like the pyrones studied by Diels and Alder[309] form mono-addition products with maleic anhydride at 110°, whereas 5,6-dialkylpyran-2-ones under these conditions give only the di-addition products[213].

Di-addition products are also formed by 5,6-dialkyl--substituted 2-pyrones containing bromine[230] or acetoxy or chloromethyl groups[224,234,235] in position 3. With polychloropyrones[311] the course of the diene synthesis depends on the number of chlorine atoms in the α-pyrone ring. Thus 3,4,5,6-tetrachloropyran-2-one forms only a di-addition product, whereas the 3,5,6-trichloro- and 3,5-dichloro-pyran-2-ones give mono- and di-addition products.

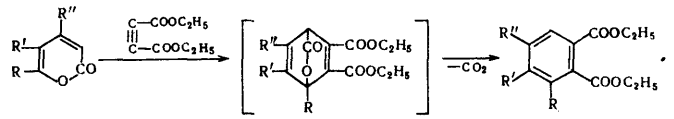
The presence in the 3 position of the α-pyrone ring of such electronegative substituents as a nitro-, sulpho-, or carboxyl group[123,231] completely deactivates the diene system of the 2-pyrones, making it incapable of undergoing the diene synthesis.

The formation of crystalline di-addition products with maleic anhydride‡, which usually occurs with excellent yields and is accompanied by the characteristic liberation of carbon dioxide, can serve as an excellent method for the identification of 2-pyrones[120,138,208,213,215].

Bu′ Lock and Smith[59] used this reaction to demonstrate the structure of the product of the methylation of 4-hydroxy--6-methylpyran-2-one, which was a mixture of the methoxy--derivatives of the corresponding γ- and α-pyrones, of which only the latter reacted with maleic anhydride:

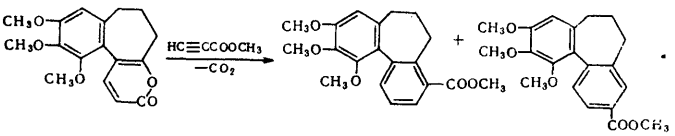


The use of diethyl butyndioate[59,312,313] as a dienophile in reaction with 2-pyrones has been described; the reaction is accompanied by the evolution of carbon dioxide and leads to the formation of the corresponding esters of phthalic acid:



This reaction was used to obtain difficultly accessible derivatives of phthalic acids[18,314].

Methyl propiolate reacts with substituted 2-pyrones to give both possible reaction products — the corresponding esters of the *ortho*- and *meta*-substituted benzoic acids[18]:

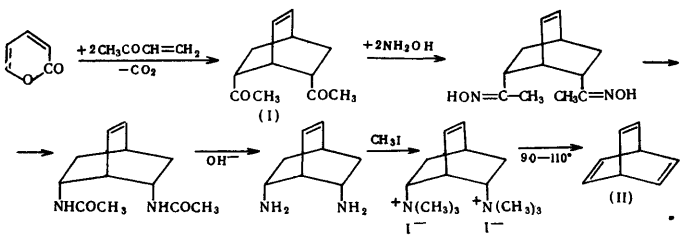


The ability of 2-pyrones to undergo the Diels–Alder reaction has recently been used in organic synthesis. Thus one of the isomeric di-addition products of 2-pyrone with

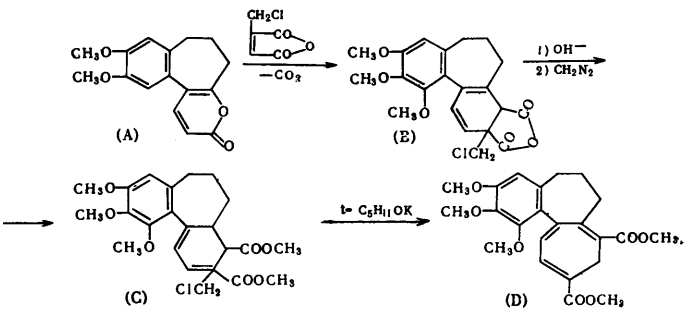
† The endo-configuration of the addition product (A) was recently confirmed by measurement of its dipole moment.[310]

‡ The formation of di-addition products was also observed in the reaction of 2-pyrones with acrylonitrile[246] and *N*-phenylmaleimide.[95]

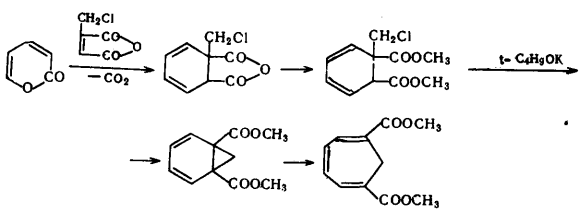
methyl vinyl ketone (I) was used in the synthesis of barrelene, bicyclo[2,2,2]octa-2,5,7-triene[19]:



The diene synthesis of the tricyclic 2-pyrone (A) with chloromethylmaleic anhydride was used to synthesise the ester (D) having the colchicine carbon skeleton[17,18]:

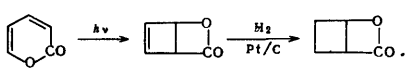


The analogous reaction of coumalin with 2-chloromethylmaleic anhydride can be used for the preparative production of cycloheptatriene-1,3-dicarboxylic acid[315]:



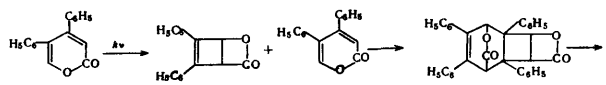
4. PHOTOISOMERISATION OF 2-PYRONES

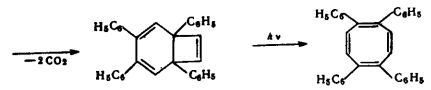
It was recently shown[316] that under the action of ultraviolet light 2-pyrone isomerises into a β-lactone condensed with a cyclobutene ring (the yield is almost quantitative); the structure of the β-lactone was confirmed by the formation of an addition product with isobenzofuran and also by hydrogenation into the corresponding saturated β-lactone:



This interesting reaction was recommended by the authors for the preparation of compounds of the cyclobutane series.

The example of 4,5-diphenylpyran-2-one showed[317] that the β-lactone formed initially undergoes a diene synthesis with the original pyrone under the conditions of the reaction to form an addition product, which on further irradiation is converted into the tetraphenylcyclo-octatetraene:





The published work on the reactivity of 2-pyrones shows that the long-held view of the 2-pyrones as doubly-unsaturated six-membered lactones does not exhaust all the peculiar properties of this heterocyclic system. Now it is also recognised to possess aromatic properties, which should be ascribed to the 2-pyrones on the basis of their recently discovered ability to undergo typical electrophilic substitutions.

The variety of chemical properties of the α-pyrone ring which is apparent in their capability for photoisomerisation, to diene synthesis, and also to react with various nucleophilic reagents (for example, the Grignard reagent, potassium cyanide), allows 2-pyrones to be widely used in organic synthesis for obtaining difficultly accessible compounds of the cyclobutane, cyclo-octatetraene, cycloheptatriene, and pyran series, derivatives of muconic acid, etc.

These results acquire greater importance in that 2-pyrones themselves, thanks to the many methods of preparation developed in recent years, have become available.

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HYDROGEN BONDS AND π-COMPLEXES IN RADICAL LIQUID-PHASE REACTIONS

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1. INTRODUCTION

The investigation of the influence of the solvent on the kinetics of radical liquid-phase reactions is of considerable importance for the theory of reactivity. The interaction of a reacting species with solvent molecules alters the electronic structure and reactivity of the species. From a knowledge of this interaction it is possible to obtain important information about the factors influencing the reactivity of the reacting species. There is, moreover, another practical aspect of this problem, associated with the choice of solvent and the improvement of technological processes.

The strongest specific interactions exerting a significant influence on the kinetics and sometimes also the mechanism of liquid-phase radical reactions are those revealed in hydrogen bonds and π-complexes. The aim of the present review is to examine the part played by these interactions in kinetics and to reveal their nature and mechanism, that is to analyse the structural-kinetic aspect of specific interactions.

2. HYDROGEN BONDS IN RADICAL REACTIONS

The problem of the part played by hydrogen bonds in the kinetics of chemical reactions was first raised by Emanuel'.[1] A later review[2] examined a large amount of material on the influence of hydrogen bonding on the kinetics and mechanism of many reactions (chiefly ionic). Numerous studies carried out since that time have confirmed conclusively that the manifestation of hydrogen bonding is one of the fundamental characteristics of liquid-phase kinetics. Much of the mechanism by which hydrogen bonding affects the rate of radical reactions is not yet clear, however.

It is first of all important to know whether a reaction takes place through equilibria involving the association of the reacting species by hydrogen bonding and if so, which of the constants of the multi-stage equilibrium are important. It is possible that the reaction involves not only free non-associated molecules, but also solvates, so that hydrogen bonding is also manifested in the activated complex. The coordination number of the solvated complex is then always of considerable importance.

Physical methods of study (X-ray diffraction, electron diffraction, infrared spectroscopy, nuclear magnetic resonance, etc.) make it possible to obtain extensive thermodynamic information on the structure of the solvates, their coordination numbers, and the equilibrium constants for a large number of classes of substances. This material has been collected in a number of reviews and monographs[3-5]. Different methods often give contradictory information on the structure of solvates, but even if the structure of the associated forms is fairly well known, it is difficult to estimate the part which they play in kinetics: for this, kinetic analysis of the influence of association on the reaction rates is necessary.

In radical reactions, each of the participants in the reaction — the molecule and the radical — may be associated. Let us consider first the influence of association of the molecules on the rate of their reactions.

In the study of the decomposition of hydroperoxides, which are the primary products of the oxidation of most organic and many inorganic compounds, it has been established that at sufficiently high concentrations of the hydroperoxide, its decomposition obeys the kinetic equation for a first-order reaction and apparently proceeds according to the scheme

$$2ROOH \rightarrow R\dot{O}_2 + H_2O + R\dot{O}. \quad (1)$$

This has been observed in the decomposition of ethyl linoleate[6], cyclohexyl[7], tetralin[8], n-decyl[9], t-butyl[10], and cumene hydroperoxides.