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THIOLACTONES

M. G. Lin'kova, N. D. Kuleshova, and I. L. Knunyants

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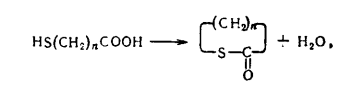
Thiolactones are internal esters of mercapto-acids. The first representatives of this class of sulphur-containing cyclic compounds were obtained towards the end of the last century. Until recently only γ- and δ-thiolactones were investigated. In 1955 β-propiothiolactone was obtained for the first time and in the same year the preparation of the simplest three-membered α-thiolactone was reported but its structure was not proved[1]. Thiolactones with rings larger than six-membered appear to be unknown.

The latest data on the structure of 2-hydroxythiophens, which are actually unsaturated γ-thiolactones, are very interesting.

The reactivity of various thiolactones is of exceptional theoretical and practical interest. Its investigation led to important findings about ring stability and bond conjugation and many new synthetic methods have been developed for mercapto-acids, amino-mercapto-acids, polypeptides containing mercapto(sulphydryl)-groups, antiradiation preparations, and new sulphur-containing polymers. Many of these classes of compounds play an important role in metabolism and exhibit interesting physiological activity.

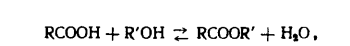
1. SATURATED γ- AND δ-THIOLACTONES

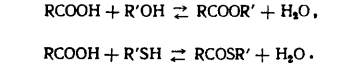
All the known synthetic methods for δ-thiolactones can be used also for γ-thiolactones, but the latter are often obtained in other ways which are unsuitable for δ-thiolactones. Since the properties of saturated γ- and δ-thiolactones are very similar, it is useful to consider them together. The most widely used method for the preparation of saturated γ- and δ-thiolactones is the direct lactonisation of γ- and δ-mercapto-acids



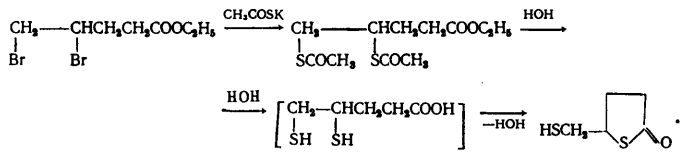
where n = 3 or 4.

"Thiolactonisation" is achieved less readily than the lactonisation of the corresponding hydroxy-acids, which usually do not exist in a free state because of the ease of cyclisation. This is consistent with the fact that the equilibrium in the esterification of acids with alcohols is displaced towards the formation of the ester to a greater extent than in the esterification of acids with mercaptans:



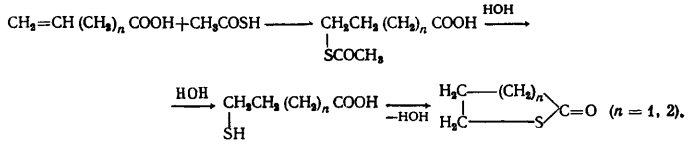


The lactonisation of mercapto-acids is accelerated by heating and in the presence of acids. Branched-chain mercapto-acids are more readily lactonised than acids with a straight chain. Five-membered γ-thiolactones are more readily formed than six-membered δ-thiolactones. This is particularly clearly seen, for example, with γδ-dimercaptovaleric acid, which cannot be isolated in a free state because of its ready cyclisation into the γ-thiolactone[2]. On the other hand, the δ-thiolactone cannot be obtained:



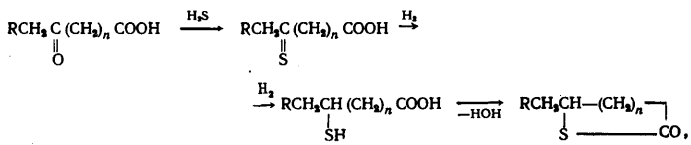
Other examples of partial or complete lactonisation of γ-mercapto-acids directly on preparation are also known. While the lactonisation of δ-mercapto-acids requires prolonged heating at a high temperature (about 270°), the preparation of γ-thiolactones often involves no more than the preparation of the γ-mercapto-acids, whose slow distillation above 100° results in lactonisation.

The most widely used general method for the preparation of γ- and δ-mercapto-acids, which consists in the addition of thioacetic acid to βγ- and γδ-unsaturated acids under free radical conditions, was proposed by Holmberg and Schjånberg[3]. Alkaline hydrolysis of the γ- and δ-acetylthio-acids formed under these conditions yields the corresponding mercapto-acids which can then be lactonised, for example:



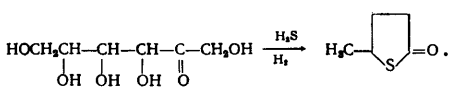
The γ- and δ-thiolactones obtained by this method are listed in the Table.

Farlow and coworkers[10-12] proposed a convenient method for the synthesis of γ- and δ-mercapto-acids, which consists in the hydrogenation of carboxylic acids, containing a thiocarbonyl group in the γ- or δ-position, in the presence of catalysts — sulphides of molybdenum, iron, etc. Usually one starts with keto-acids which are hydrogenated in the presence of hydrogen sulphide, carbon disulphide, or sulphur (reductive thiolation). Application of this method to levulinic, γ-oxopimelic, and γ-acetylbutyric acids yielded the corresponding mercapto-acids, which under the conditions of the reaction are almost completely converted into the γ- and δ-thiolactones:



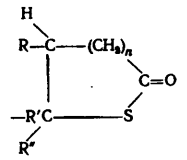
where n = 2 and R = H or CH_2COOH, or n = 3 and R = H.

The formation of γ-methyl-γ-butyrothiolactone in reductive thiolation of D-fructose has also been described[13]:



The mechanism of this reaction is obscure.

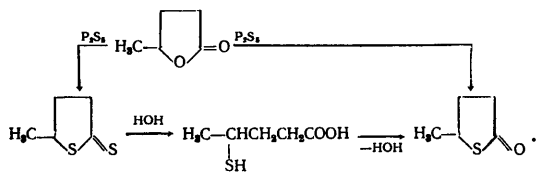
TABLE.



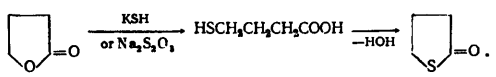
n	R	R′	R″	References
1	H	H	$CH(CH_3)_2$	4
1	H	CH_3	$CH(CH_3)_2$	4
1	H	H	CH_3	5
1	COOH	H	H	6
1	H	H	H	3,7
1	H	H	C_2H_5	8
2	H	H	H	5,8,9
2	CH_3	CH_3	CH_3	4

A method has also been proposed for the conversion of γ- and δ-lactones into the corresponding thiolactones by heating with carbon disulphide[14] or derivatives of thiocarbonic acid[15] [CS_2, COS, $CS(NH_2)_2$, and others], but it does not always give satisfactory results[16,17].

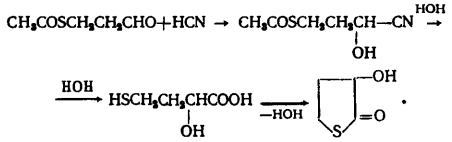
Yur'ev[18] achieved the reaction between γ-butyrolactone and hydrogen sulphide at 350° over alumina and obtained γ-butyrothiolactone in high yield. The conversion of γ-methyl-γ-butyrolactone into a mixture of γ-methyl-γ-butyrothiolactone and γ-methyl-γ-butyrodithiolactone on heating with phosphorus pentasulphide has been described; γ-methyl-γ-butyrodithiolactone yields γ-mercaptovaleric acid on alkaline hydrolysis, the latter being subsequently converted into the γ-methyl-γ-butyrothiolactone[19]:



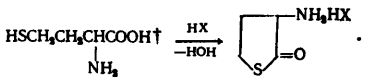
By cleaving γ-butyrolactone with potassium hydrogen sulphide, Reppe *et al.*[20] isolated γ-mercaptobutyric acid, which they dehydrated to γ-butyrothiolactone. Kharasch[21] obtained the same result on cleaving γ-butyrolactone with sodium thiosulphate; in this case the first stage is the formation of Bunte's salt:



The lactonisation of substituted γ-mercapto-acids takes place even more readily than that of γ-mercaptobutyric acid. It has already been pointed out that γδ-dimercaptovaleric acid spontaneously cyclises into γ-mercaptomethyl-γ-butyrothiolactone (see above). α-Hydroxy-γ-mercaptobutyric acid cyclises just as easily[22]:

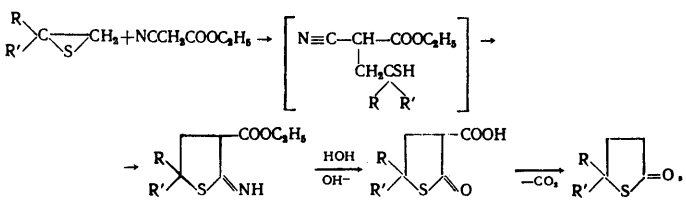


In the presence of acids homocysteine readily forms α-amino-γ-butyrothiolactone [23,24]:



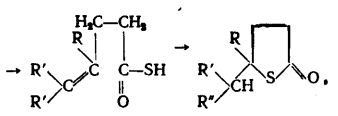
N-acylated homocysteine thiolactone can be obtained similarly or by acylation of homocysteine thiolactone itself [25].

Snyder and Alexander [28] proposed a novel method for the preparation of γ-thiolactones from thioepoxides and cyanoacetic ester:



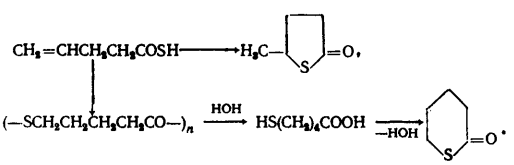
where R = R′ = H, R = H and R′ = CH_3, or R = R′ = CH_3. [29]

Korte and Christoph [4] found that γδ-unsaturated carbothiolic acids spontaneously cyclise into γ-thiolactones:

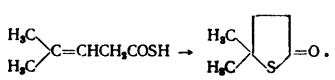


where R = H and R′ = R″ = CH_3, R = R′ = R″ = CH_3, and R = R′ = R″ = H. The analogous isomerisation of unsaturated carboxylic acids takes place under more severe conditions, contrary to the usual finding that lactones are formed more readily than thiolactones. δ-Thiolactones cannot be obtained in this way.

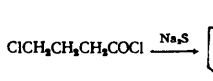
In addition to γ-methyl-γ-butyrothiolactone, allylthioacetic acid yields a linear polythioester, whose hydrolysis leads to the formation of δ-mercaptobutyric acid, which lactonises into δ-valerothiolactone [4]:



The cyclisation of βγ-unsaturated carbothiolic acids has been studied in only one case. As with γδ-unsaturated carbothiolic acids, the γ-thiolactone was obtained [4]:

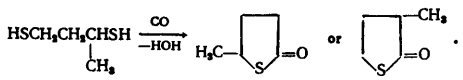


The preparation of γ-butyrothiolactone from γ-chlorobutyryl chloride and sodium sulphide in 71% yield has been described [30,31]:



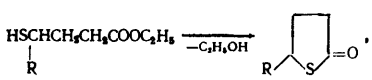
† The initial homocysteine is obtained by demethylation of methionine with hydriodic acid, debenzylation of *S*-benzylhomocysteine with sodium in liquid ammonia [23-26], or by reduction of homocystine [23,27].

When butane-1,3-dithiol reacts with carbon monoxide in the presence of cobalt carbonyl, α(or γ)-methyl-γ-butyrothiolactone forms in 15% yield [32]:



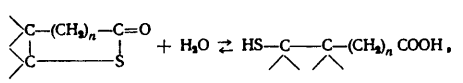
The position of the methyl group has not been established.

Two cases of formation of γ-thiolactones on distillation of γ-mercapto-carboxylic acid esters have been described:



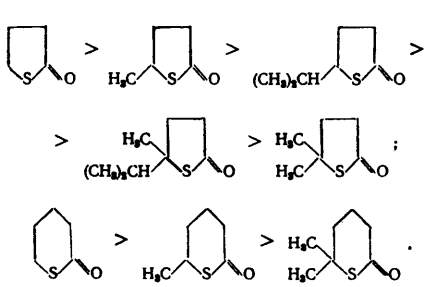
where R = H [7] or R = $CH_2CH_2COOC_2H_5$. [11]

Among the chemical properties of γ- and δ-thiolactones, hydrolysis has been most thoroughly investigated. On hydrolysis of γ- and δ-thiolactones, the ring always splits at the S–acyl bond and the corresponding mercapto-acids are formed. The hydrolysis of γ-thiolactones is reversible while δ-thiolactones are almost completely hydrolysed:



where *n* = 1 or 2. The hydrolysis of γ- and δ-thiolactones is accelerated by acids and especially by bases [5,6,33].

The splitting of substituted thiolactones, including hydrolytic splitting, is more difficult than in the case of unsubstituted thiolactones, *i.e.* the stability of the ring increases with the number of substituents (p. 494). Thus Korte and Christoph [4] found that the rate of alkaline hydrolysis decreases in the following sequences:



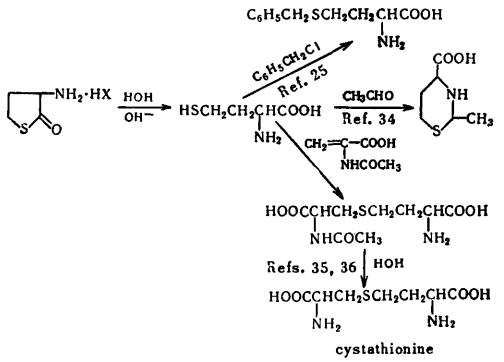
Stevens and Tarbell [29] found that the rate of alkaline hydrolysis of γ- and δ-thiolactones and their oxygen analogues is less sensitive to changes in structure than the rate of hydrolysis of open-chain esters and thioesters. Thus ethyl acetate is hydrolysed 100 times faster than t-butyl acetate. On the other hand, γ-butyrolactone is hydrolysed only eight times faster than γγ-dimethyl-γ-butyrolactone. This relation between the rates of alkaline hydrolysis holds also for thioesters and thiolactones.

The authors' explanation of this finding is that the cyclic structure ensures a relatively fixed position of the carbonyl group, so that the possibility of nucleophilic attack on this group changes little when substituents are introduced in the vicinity of the reaction centre; on the other hand, in esters

and thioesters introduction of substituents gives rise to steric hindrance and impedes the attack of the nucleophilic agent on the carbonyl group.

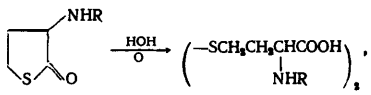
After hydrolysis of substituted γ-thiolactones, it is in many cases impossible to isolate the corresponding γ-mercapto-acids, since on acidification they readily recyclise into the thiolactones [4,20,22,29]. Thus, it is virtually impossible to isolate homocysteine after hydrolysis of homocysteine thiolactone.

The ease of alkaline hydrolysis of homocysteine thiolactone makes it possible to employ it as a source of homocysteine, which is otherwise difficult to obtain:

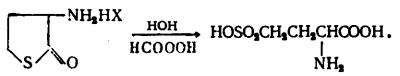


Since homocysteine thiolactone and its *N*-acetyl derivatives are active antiradiation agents‡, studies of the hydrolysis of this substance have a bearing on the problem of the relation between the protective properties of substances and their structure [34,37-41].

Hydrolysis of γ-thiolactones in the presence of oxidising agents yields disulphides of γ-mercapto-acids [28,42,43]. Thus, on alkaline hydrolysis of homocysteine thiolactone in the presence of atmospheric oxygen, homocystine is formed [25]:

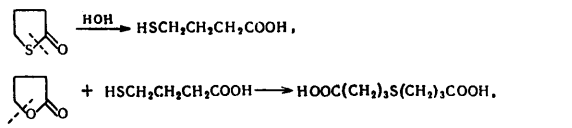


where R = H or COC_6H_5. Hydrolysis of homocysteine thiolactone in the presence of hydrochloric and performic acids gives homocysteic acid [44]:

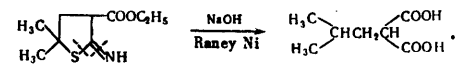


Some reactions of γ-thiolactones and their derivatives can only be understood by assuming that the first stage of the reaction involves hydrolytic opening of the thiolactone ring at the S–acyl bond.

Reppe and coworkers [20,45,46] described the reaction of thiolactones with lactones in the presence of alkali. The authors are clearly wrong in interpreting this reaction as splitting of the thiolactone by the salt of the hydroxy-acid formed on alkaline hydrolysis of the lactone. It is evident that the alkali hydrolyses the thiolactone and the salt of the mercapto-acid thus formed splits the lactone at the O–acyl bond:

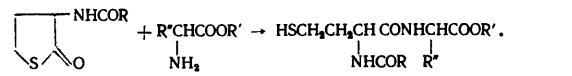


Elimination of sulphur from 3-ethoxycarbonyl-2-imino--5,5-dimethylthiophan with Raney nickel in the presence of alkali [28] gave isobutylmalonic acid:

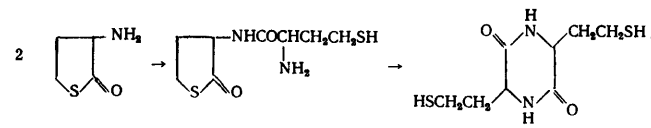


This could only occur after preliminary hydrolytic splitting of the thiolactone ring at the S–acyl bond. Otherwise elimination of sulphur would have given rise to an aldehyde group.

Aminolysis of γ-thiolactones has been investigated with homocysteine thiolactone as an example. *N*-acyl homocysteine thiolactone is split by α-amino-acid esters under mild conditions [42]:

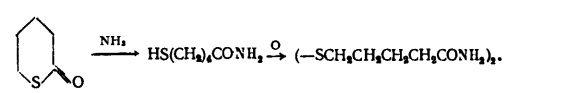


The aminolysis of *N*-acetylhomocysteine thiolactone with glycylglycine and ε-aminocaproic acid has been described [44]. The acylating capacity of *N*-acyl homocysteine thiolactone is used in peptide synthesis and for introduction of sulphur into proteins [47-49]. Homocysteine thiolactone exists only in the form of hydrogen halides or *N*-acyl derivatives. When an attempt is made to obtain homocysteine thiolactone with a free amino-group, mutual aminolysis of two molecules of homocysteine thiolactone takes place with formation of 3,6-di-(β-mercaptoethyl)-2,5-dioxopiperazine [24]:

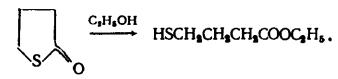


The latter is readily oxidised to a polymeric product.

The aminolysis of δ-thiolactones has been described in only one case: δ-valerothiolactone gave the amide of δ-mercaptovaleric acid, which is readily oxidised to the corresponding disulphide [33]:



The alcoholysis of δ-thiolactones has not been investigated, but the splitting of γ-butyrothiolactone with ethanol in the presence of sodium ethoxide has been described:

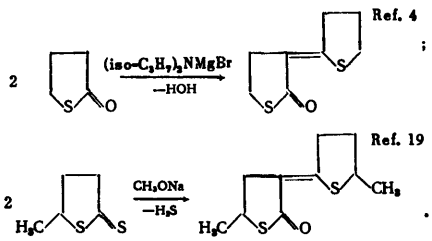


Thus in hydrolysis, aminolysis, and alcoholysis δ- and γ-thiolactones are split at the S–acyl bond.

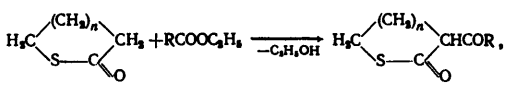
‡ *N*-Carbamoylhomocysteine thiolactone does not exhibit protective antiradiation properties [34].

The reduction of γ-butyrothiolactone to thiophan with zinc amalgam in dilute hydrochloric acid, described by Yur'ev[18], characterises the reactivity of the carbonyl group.

Like γ-lactones, γ-thiolactones and γ-dithiolactones undergo self-condensation in the presence of alkaline catalysts:

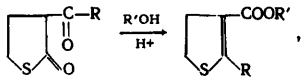


The result of the presence of an active methylene group, γ- and δ-thiolactones, like their oxygen analogues, are capable of undergoing ester condensation in the presence of basic catalysts:

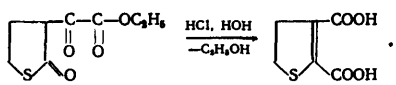


where n = 1 or 2.

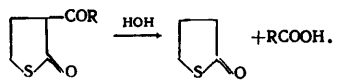
Since γ- and δ-thiolactones are readily split by alkaline reagents, application of the usual Claisen condensation catalysts (C_2H_5ONa, NaH, Na) results in low yields of the condensation products. The best catalyst for the Claisen condensation involving γ- and δ-thiolactones is diisopropylaminomagnesium bromide $(iso\text{-}C_3H_7)_2NMgBr$.[7,9,16] The α-acyl-γ- and α-acyl-δ-thiolactones undergo the so-called acyllactone rearrangement in the presence of hydrogen chloride[4,16,17]. Thus, in the cold in alcohols saturated with hydrogen chloride, α-acyl-γ-thiolactones form esters of dihydrothiophen-3-carboxylic acid in good yields:



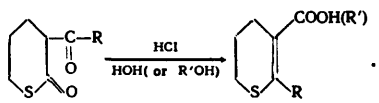
where R = H and R′ = CH_3, R = R′ = CH_3, and R = $COOC_2H_5$ and R′ = C_2H_5. When R = $COOC_2H_5$, the rearrangement takes place also in the presence of hydrochloric acid:



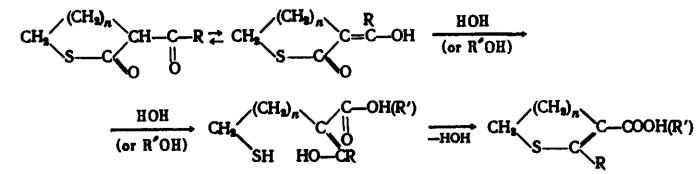
However, when R = H or CH_3, hydrochloric acid causes the acid hydrolysis characteristic of β-keto-esters:



α-Acyl-δ-thiolactones rearrange even more readily than α-acyl-γ-thiolactones. In the presence of hydrochloric acid dihydrothiopyran-3-carboxylic acids are formed and in the presence of alcohol saturated with hydrogen chloride the esters of these acids[16]:

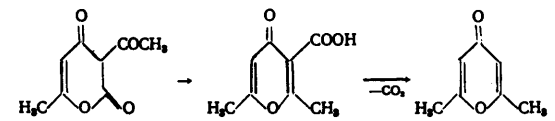


The acyllactone rearrangement is a convenient method for the preparation of dihydrothiophen- and thiopyran-carboxylic acids, which are difficult to obtain. The rearrangement involves the enolisation of the α-acylthiolactone, which is characteristic of β-keto-esters, and solvolytic splitting of the thiolactone ring at the S–acyl bond (hydrolysis or alcoholysis) with subsequent elimination of water[4,17]:

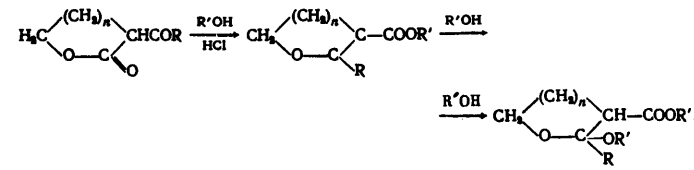


where n = 1 or 2.

The acyllactone rearrangement has also been studied in detail for γ- and δ-lactones. A generally familiar example of the rearrangement of a δ-lactone is the conversion of dehydroacetic acid into αα′-dimethyl-γ-pyrone:



The rearrangement of α-acyl-γ- and α-acyl-δ-lactones in alcohol usually results in saturated systems because of the addition of the alcohol to the double bond:



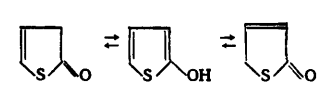
where n = 1 or 2.

However, alcohol does not add to the products of the acyllactone rearrangement of thiolactones either under the conditions of the rearrangement or under more severe conditions. Korte and coworkers explain this difference by the fact that the free electron pair of the sulphur atoms shows a greater tendency towards conjugation with the π electrons of the double bond than the electron pair of the oxygen atom.

2. UNSATURATED γ-THIOLACTONES AND γ-THIOLACTONES CONDENSED WITH A BENZENE RING

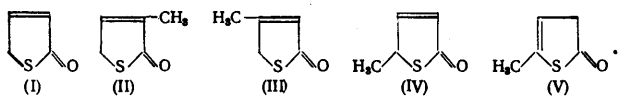
Unsaturated γ-Thiolactones

Unsaturated γ-thiolactones are tautomeric forms of 2-hydroxythiophen:



Infrared and nuclear magnetic resonance spectroscopy showed that 2-hydroxythiophen and its derivatives virtually do not exist in the hydroxy-form[50]. Thus unsubstituted 2-hydroxythiophen exists exclusively as the thiolactone (I), 2-hydroxy-3-methylthiophen consists of virtually the pure

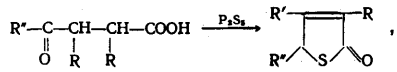
thiolactone (II), and 2-hydroxy-4-methylthiophen also exists only as the unsaturated thiolactone, the double bond being located between positions 3 and 4 in this case too[51] [thiolactone (III)]. Both thiolactone forms [(IV) and (V)] of 2-hydroxy-5-methylthiophen were isolated and their interconversion was achieved. The hydroxy-form of any of the above compounds could not be isolated.



(I) (II) (III) (IV) (V)

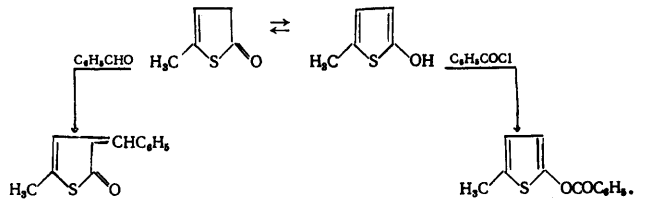
Only in the case of 2-hydroxy-5-phenylthiophen was the hydroxy-form detected spectroscopically in alcohol solution[52]. Clearly, the reason for the stability of the hydroxy--form in this case is the formation of a conjugated system with the benzene ring and the high polarity of the solvent. In chloroform solution of 2-hydroxy-5-phenylthiophen the hydroxy-group can no longer be detected, and only the carbonyl group is found. Probably, 2-hydroxy-5-phenylthiophen exists as a tautomeric equilibrium mixture, the equilibrium being displaced towards the hydroxy-form in polar solvents. Thus 2-hydroxy-5-phenylthiophen is the only 2-hydroxythiophen whose generally accepted name to some extent corresponds to its structure. In all other cases one should refer to unsaturated γ-thiolactones rather than 2-hydroxythiophens. It is in fact the inability of "2-hydroxythiophen" to exist in the hydroxy-form that is responsible for the profound difference between the properties of these and phenols. While the physical properties of 2-methoxythiophen and anisole are as similar as those of thiophen and benzene, "2-hydroxythiophen" and phenol differ sharply from one another in both physical and chemical properties[53]. In contrast to phenols, "2-hydroxythiophens" are unstable and difficult to obtain.

The first attempts to obtain derivatives of "2-hydroxythiophen" were made in the eighties of the previous century. Kues and Paal[54-57] used a method for the preparation of "2-hydroxythiophen" derivatives analogous to the classical synthesis of thiophen from succinic acid and phosphorus trisulphide. By heating together γ-keto-carboxylic acids and phosphorus pentasulphide, the above workers obtained substituted "2-hydroxythiophens" in low yields§:

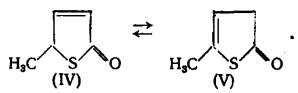


where R = R′ = H and R″ = CH_3, R = R′ = H and R″ = C_6H_5, R = H and R′ = R″ = CH_3, and R = R″ = CH_3 and R′ = H. However, later attempts to repeat these syntheses were not always successful[52].

In 1939 Steinkopf and Thormann[58], in an attempt to prepare "2-hydroxy-5-methylthiophen", modified somewhat the method of Kues and Paal and obtained a substance with a boiling point different from that of the "2-hydroxy-5-methylthiophen" which the earlier workers synthesised. The boiling point of the substance prepared by Steinkopf and Thormann was close to that of *p*-cresol and gave a benzylidene derivative. The above workers therefore decided that they were the first to obtain 2-hydroxy-5-methylthiophen. They explained the formation of the benzylidene derivative on reaction with benzaldehyde by the existence of a tautomeric equilibrium:



It was not until 1960 that Gronowitz and Hoffman[50] succeeded in repeating the experiments of Kues and Paal and established the structure of "2-hydroxy-5-methylthiophen" (thiotenol). They showed that under the usual conditions "2-hydroxy-5-methylthiophen" consists of an equilibrium mixture of two thiolactone forms: 85% of (IV) and 15% of (V):

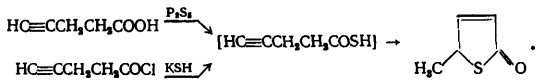


(IV) (V)

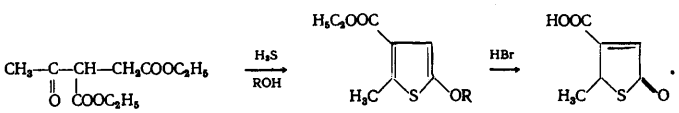
Form (V) is the less stable of the two¶.

Kues and Paal obtained the thiolactone (V) while Steinkopf and Thormann prepared the isomeric form (IV), but uncritical use of chemical reactions for the determination of the structure of "2-hydroxy-5-methylthiophen" led them to an erroneous conclusion†.

"2-Hydroxy-5-methylthiophen" (IV) was also prepared by the isomerisation of but-3-yncarbothiolic acid[60]:

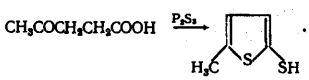


"2-Hydroxy-5-methylthiophen-4-carboxylic acid" was obtained by the action of hydrogen sulphide on the ester of β-ethoxycarbonyllevulinic acid[61]:

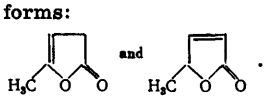


In all the methods for the preparation of substituted "2-hydroxythiophens" considered above the starting materials were open-chain compounds. However, methods

§ Reaction of levulinic acid with phosphorus trisulphide yields 2-mercapto-5-methylthiophen, which exists predominantly in the thiol form[50]:



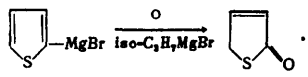
¶ The oxygen analogue of 2-hydroxy-5-methylthiophen also exists in two lactone forms:



The first of these (α-Angelica lactone) is less stable than the second (β-Angelica lactone).

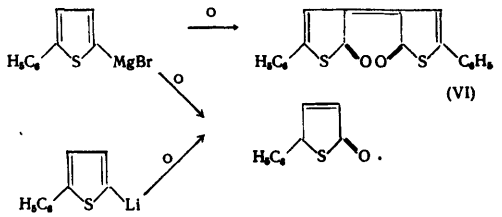
† Demerseman and coworkers[59] assert that "2-hydroxy-5--methylthiophen" contains more than 90% of the unsaturated thiolactone with the double bond between positions 4 and 5 [form (V)], and they completely disregarded the second thiolactone form.

have also been developed for the introduction of a hydroxy--group into the thiophen ring. Thus in 1950 Hurd and Kreuz [53] were the first to obtain unsubstituted "2-hydroxythiophen" by oxidising with oxygen 2-thienylmagnesium bromide in the presence of more than an equivalent amount of isopropylmagnesium bromide:

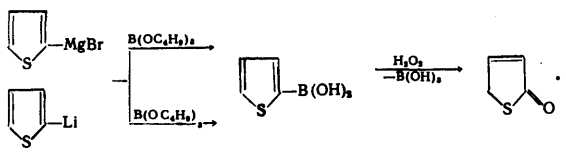


When peroxides are used as oxidising agents, the yield of "2-hydroxythiophen" is reduced [62].

Oxidation of 5-phenylthien-2-ylmagnesium bromide and 5-phenylthien-2-yllithium under the same conditions gave "2-hydroxy-5-phenylthiophen" in 30% yield [63]. The bisthiolactone (VI) was obtained from 5-phenylthien-2-ylmagnesium bromide as a side product:

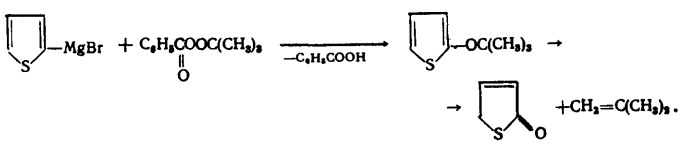


Reaction of thiophen metal-substituted in the 2-position with tributyl borate at -70° yielded 2-thienylboronic acid, whose oxidation with hydrogen peroxide is a convenient method for the preparation of "2-hydroxythiophen" [51]:

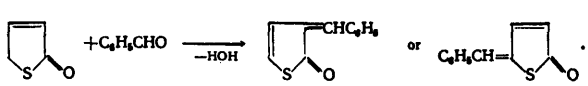


Apart from "2-hydroxythiophen", "2-hydroxy-5-methylthiophen" and the previously unknown "2-hydroxy-3-methylthiophen" and "2-hydroxy-4-methylthiophen" were obtained in good yields by this method.

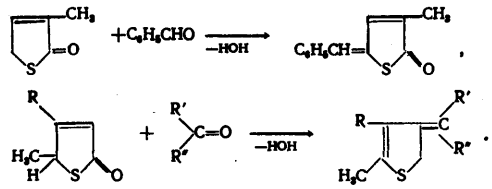
The best method for the synthesis of "α-hydroxythiophen" (70% yield) is pyrolysis of 2-t-butoxythiophen in the presence of *p*-toluenesulphonic acid [63]:



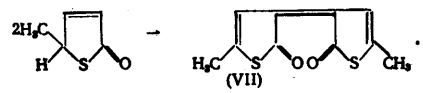
"2-Hydroxythiophens" are very unstable compounds. They readily resinify on being stored in air and undergo particularly rapid decomposition in the presence of alkalis, alcohols, and amines. On the other hand, "2-hydroxythiophen" remains virtually unchanged on being boiled at 219° in a stream of nitrogen [53]. "2-Hydroxythiophens" undergo condensation with carbonyl compounds. For example, with benzaldehyde a benzylidene derivative is obtained:



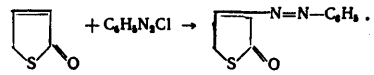
Substituted "2-hydroxythiophens" react similarly with aldehydes and ketones:



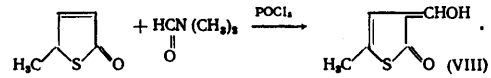
The oxidation of "2-hydroxy-5-methylthiophen" with ferric chloride to the bisthiolactone (VII) has been described [58]:



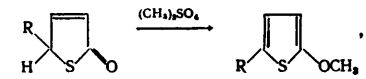
"2-Hydroxythiophen" undergoes azo-coupling [53]:



"2-Hydroxy-5-methylthiophen" reacts with dimethylformamide in the presence of phosphorus oxychloride with the formation of "3-formyl-2-hydroxy-5-methylthiophen"; the product does not give reactions characteristic of the aldehyde group, which appears to favour the thiolactone (VIII) structure [59]:

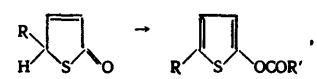


"2-Hydroxythiophens" cannot be alkylated with alkyl halides or diazomethane [52,53,59], but with dimethyl sulphate the corresponding 2-methoxy-derivatives can be obtained from "2-hydroxythiophen" and "2-hydroxy-5-methylthiophen" [53,59]:



where R = H or CH_3.

When acted upon by acylating agents (acetic anhydride, benzoyl chloride), "2-hydroxythiophens" give the acylated derivatives [52,55,58,60]:



where R = H, CH_3, or C_6H_5, and R′ = CH_3 or C_6H_5.

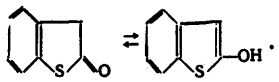
"2-Hydroxythiophens" give a colour with ferric chloride and dissolve in alkalis in the cold. They can be regenerated by passing CO_2 through the alkaline solution, but about 50% of the substance is lost, apparently as a result of ring rupture.

Thus "2-hydroxythiophens" undergo reactions characteristic of the hydroxy-form and both thiolactone forms. However, physical methods as a rule fail to confirm the hypothesis of the tautomerism of "2-hydroxythiophens".

Evidently the dual reactivity of "2-hydroxythiophens" is to be explained by migration of the reaction centre.

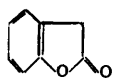
γ-Thiolactones Condensed with a Benzene Ring

Thio-oxindole is a tautomeric form of 2-hydroxythianaphthen:



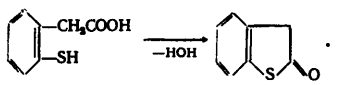
Because of the absence of spectroscopic data, the structure of thio-oxindole is still not completely clear. Two crystalline forms of thio-oxindole melting at 33–34° and 44–45° have been described‡[64]. The data on the interconversion of these forms are very contradictory. However, it is known that, when crystals of a given modification are added to fused thio-oxindole, the form with the required melting point can be obtained[65]. For this reason, the hypothesis[66] that one of the forms is 2-hydroxythianaphthen and the other thio-oxindole is not well founded.

It is most likely that the two forms of thio-oxindole are different crystalline modifications. The oxygen analogue of thio-oxindole, isocoumaranone (IX), also exists in two crystalline modifications:



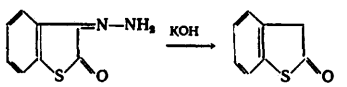
(IX).

Marschalk[67] was the first to obtain unsubstituted thio-oxindole by dehydration of *o*-mercaptophenylacetic acid:



Lactonisation takes place on heating or under the action of dehydrating agents§[67].

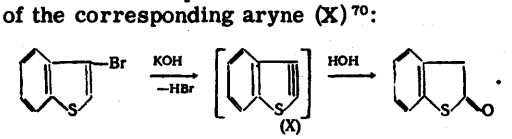
Thio-oxindole also forms when the β-hydrazone of thianaphthenquinone undergoes the Kishner reaction[64,65]:



Kommpa[68] obtained thio-oxindole by heating *o*-methylthiophenylacetyl chloride with aluminium chloride in xylene:

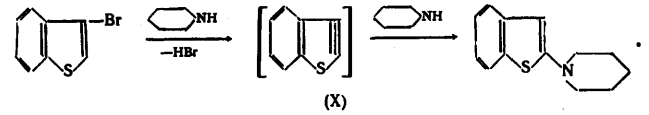


The same worker[68,69] described the formation of thio-oxindole as a result of the reaction of 3-bromothianaphthen with alcoholic caustic potash at about 200° and a pressure of 50 atm. The reaction proceeds *via* the intermediate formation of the corresponding aryne (X)[70]:



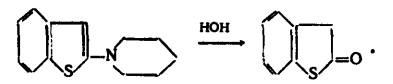
(X)

The same intermediate (X) is formed in the reaction between 3-bromothianaphthen and piperidine[70]:

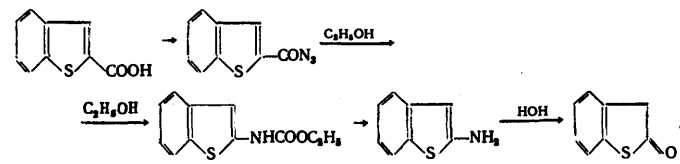


(X)

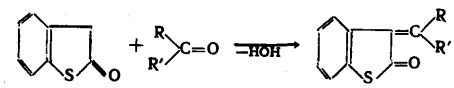
Hydrolysis of the resulting 2-piperidinothianaphthen yields thio-oxindole[71]:



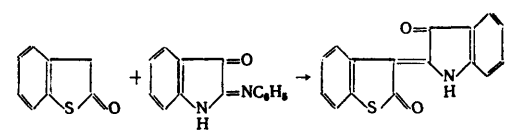
Thio-oxindole can also be obtained from thianaphthen-2-carboxylic acid by the Curtius reaction followed by hydrolysis of the amine formed[72]:



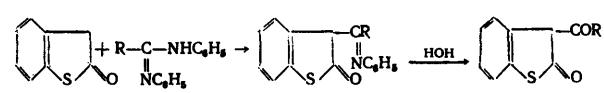
Numerous reactions of thio-oxindole reflect the mobility of the hydrogen atom in position 3.[73,74] Thio-oxindole readily reacts with carbonyl compounds[64,67,75]:



Even easier is the condensation of thio-oxindole with the anils of carbonyl compounds[67,75,76], for example:

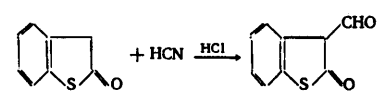


NN'-Diphenylamidines acylate thio-oxindole in position 3:[65]

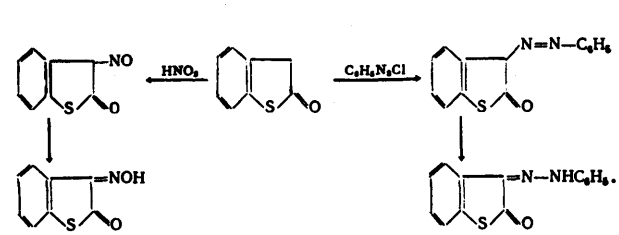


where R = H or CH_3.

3-Formylthio-oxindole was obtained by formylating thio-oxindole by the Gattermann–Koch reaction[65]:



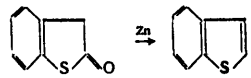
The formation of a nitroso-derivative of thio-oxindole and its azo-coupling with phenyldiazonium chloride has been described[64]:



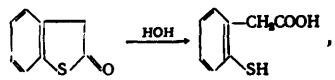
‡ 6-Ethoxythio-oxindole is also known in two forms melting at 39–40° and 47–48°.[65]

§ Because of its ready lactonisation, *o*-hydroxyphenylacetic acid does not exist in a free state[67].

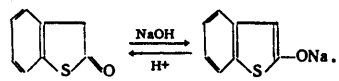
Reduction of thio-oxindole with powdered zinc yields thianaphthen[64]:



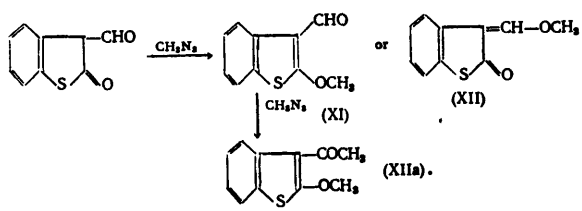
Alkaline hydrolysis of thio-oxindole with heating gives *o*-mercaptophenylacetic acid[67,68,71]:



but thio-oxindole can be regenerated by acidifying the solution after it has been dissolved in cold alkali[64]:

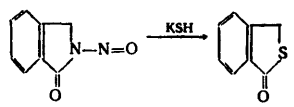


3-Formylthio-oxindole could not be alkylated either with methyl iodide or with dimethyl sulphate. Reaction with diazomethane gave a product with structure (XI) or (XII). A dimethylated derivative, to which structure (XIIa) was ascribed, forms as a side-product[65]:

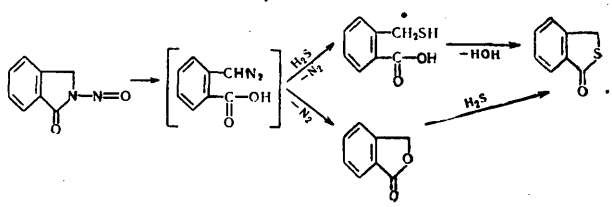


2-Thiophthalide. This γ-thiolactone, condensed with the benzene ring, is an isomer of thio-oxindole, but does not exhibit dual reactivity because of the absence of the hydrogen atom in the α-position with respect to the carbonyl group. It is a normal thiolactone, known in the literature under the name 2-thiophthalide, and was the first γ-thiolactone to be described.

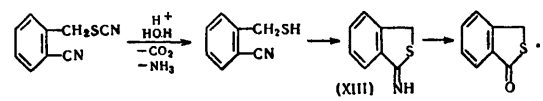
It was first obtained by Graebe[77] by treatment of *N*-nitrosophthalimidine with potassium or sodium hydrogen sulphide:



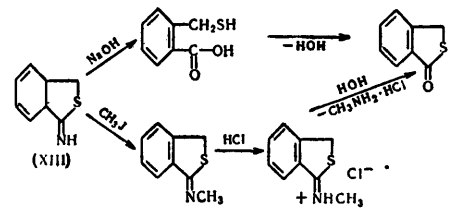
It may be supposed that the reaction involves the intermediate formation of a diazo-compound:



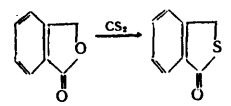
Day and Gabriel[78] obtained 2-thiophthalide by the action of concentrated hydrochloric acid on *o*-thiocyanatomethylbenzonitrile, 1-imino-2-thiophthalide (XIII) being formed as an intermediate:



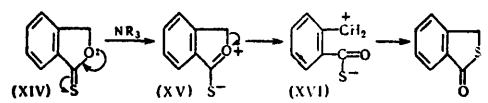
The same workers[78] obtained 2-thiophthalide from 1-imino-2-thiophthalide by other pathways:



A patent[15] describes the synthesis of 2-thiophthalide by heating phthalide with derivatives of thiocarbonic acid [CS_2, HSCN, $CS(NH)_2$, and others] in an alkaline medium:



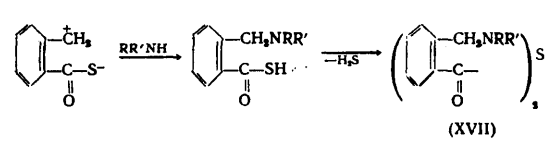
Prey and coworkers[79,80] obtained 2-thiophthalide in high yield by the rearrangement of 1-thiophthalide (XIV) in the presence of amines. They suggested the following mechanism for the rearrangement:



By virtue of its free electron pair, the amine enhances the polarisation of 1-thiophthalide and tends to stabilise the dipolar ion (XV) which undergoes "thermal" ring-opening with the formation of the betain structure (XVI); the latter is then converted to the more stable 2-thiophthalide.

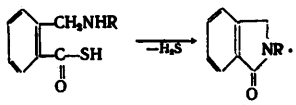
The occurrence of the stage involving the "thermal" formation of the betain (XVI) has been confirmed by measurements of the electrical conductivity of 1-thiophthalide in pyridine. Below 100° the conductivity of the solution remained unchanged and the initial 1-thiophthalide was isolated. At 100° the conductivity increased, after which 2-thiophthalide was isolated from solution.

When secondary amines are used, the betain (XVI) can be stabilised by the addition of the amine, the resulting carbothiolic acid being then converted to the diacylsulphide (XVII):

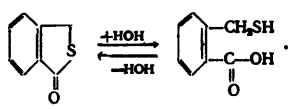


The latter is in many cases isolated as a side-product. When a primary amine or ammonia is used, an *N*-substituted phthalimidine, the product of the intramolecular

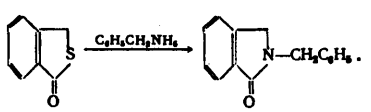
acylation of the amino-group of the carbothiolic acid, is isolated in addition to the diacylsulphide:



The properties of 2-thiophthalide have been very little investigated. Its alkaline hydrolysis yields a γ-mercapto--acid[77], which on heating is reconverted into 2-thiophthalide:

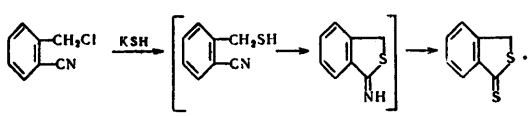


When 2-thiophthalide is heated with benzylamine under pressure, *N*-benzylphthalimidine is obtained[79]:

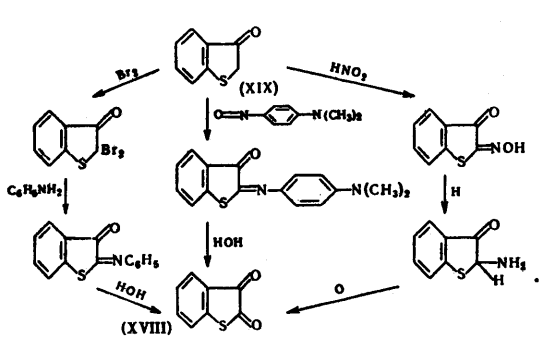


The mechanism of this reaction has not been studied.

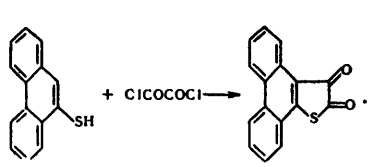
In an attempt to prepare 2-thiophthalide from *o*-cyanobenzyl chloride and potassium hydrogen sulphide, Gabriel and Leupold[81] obtained 1,2-dithiophthalide:



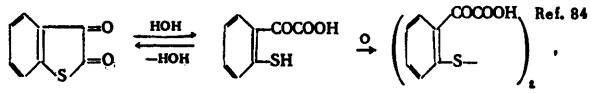
Thianaphthenquinone (XVIII) is α-oxo-γ-butyrothiolactone condensed with the benzene ring. Usually thianaphthenquinone and its derivatives are obtained by indirect oxidation of thioindoxyl (XIX)[82]:

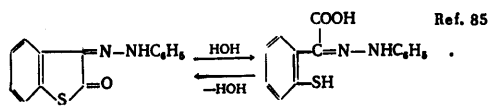


The formation of thianaphthenquinone derivatives from oxalyl chloride and thiophenol derivatives has been described[83], for example:

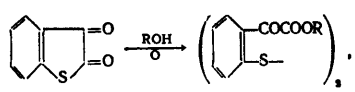


The hydrolysis of thianaphthenquinone and its derivatives involves ring rupture at the S–acyl bond. The γ-mercapto-acids thus formed are readily oxidised to the corresponding disulphides, which on heating are reconverted into the initial thiolactone:

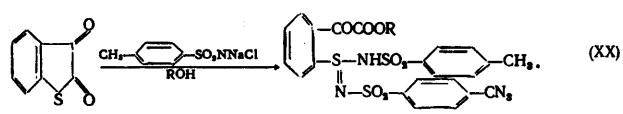




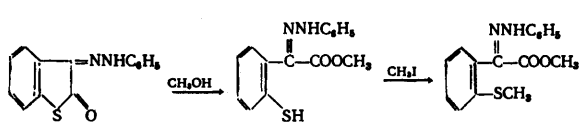
Like the hydrolysis, the alcoholysis of thianaphthenquinone proceeds with ring rupture at the S–acyl bond. Thus on heating thianaphthenquinones, containing various substituents in the ring, with alcohols in the presence of chloramine-T, the disulphides related to the corresponding thiols were obtained[86]:



where R = CH_3, C_2H_5, and C_3H_7. A more highly oxidised compound (XX) is obtained as a side-product:

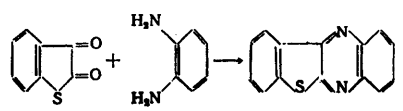


In the presence of sodium methoxide the β-phenylhydrazone of thianaphthenquinone is also split by methanol at the S–acyl bond; after treatment with methyl iodide, the phenyl hydrazone of methyl *o*-methylthiophenylglyoxylate was isolated[85]:

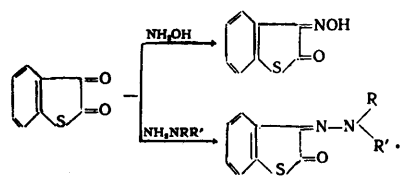


The aminolysis of thianaphthenquinone has not been studied.

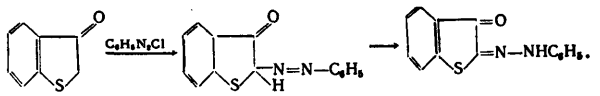
o-Phenylenediamine does not split the thiolactone ring the quinoxaline derivative of thianaphthenquinone being formed[82]:



The usual carbonyl reagents give derivatives of the β-carbonyl group of thianaphthenquinone only:



The corresponding derivatives of the α-carbonyl group can be obtained only by indirect pathways from thioindoxyl[85] (see p. 502), for example:

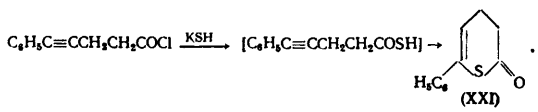


Thianaphthenquinone readily reacts with compounds containing an active methylene group[65,87,88], the reaction involving an α- or β-carbonyl group of thianaphthenquinone[89,90].

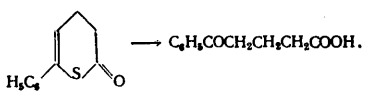
3. UNSATURATED δ-THIOLACTONES AND δ-THIOLACTONES CONDENSED WITH A BENZENE RING

Unsaturated δ-Thiolactones

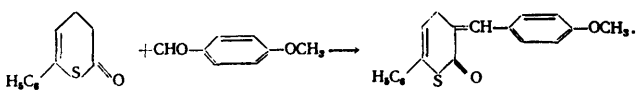
δ-Phenyl-δ-valerothiolactone (XXI) with a double bond in the γδ-position was obtained by the reaction of the chloride of 4-phenylbut-3-ynecarboxylic acid with potassium hydrogen sulphide. Evidently, 4-phenylbut-3-ynecarbothiolic acid is formed as an intermediate[60]:



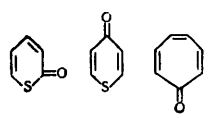
It is interesting that under the same conditions the unsaturated γ-thiolactone is formed from the chloride of the unsubstituted but-3-ynecarboxylic acid[60] (see p. 498). The structure of δ-phenyl-δ-valerothiolactone (XXI) was confirmed by its hydrolysis with 50% sulphuric acid to γ-benzoylbutyric acid:



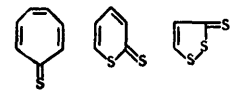
The condensation of δ-phenyl-δ-valerothiolactone with anisaldehyde has been described:



When a second double bond is introduced into the ring of an unsaturated δ-thiolactone, its thiolactone properties recede into the background, those associated with the conjugation of the free electron pair of the sulphur atom with the π electrons of the double bond coming to the fore. Thus the physical and chemical properties of α-thiopyrone resemble those of the isomeric γ-thiopyrone:

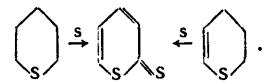


The distribution of electrons in α- and γ-thiopyrones is similar to that in tropone. These three isoelectronic compounds should have similar physical properties, which is usually found to be the case when the –CH=CH– group is replaced by –S–. Quantum-mechanical calculations and investigation of the chemical properties of α-thiopyrone confirmed that it is a pseudotropone. The above considerations apply also to α-dithiopyrone which should occupy an intermediate position between the hypothetical tropothione and "trithione", which exhibit aromatic properties.

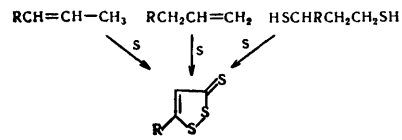


The investigation of α-thio- and α-dithio-pyrones was begun recently by Mayer and coworkers. The available data suggest that these compounds are aromatic.

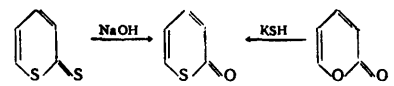
α-Dithiopyrone was obtained by the reaction of thiacyclohexane or thiacyclohexene with sulphur at a high temperature (about 200°)[91-93]:



This method resembles those for the preparation of "trithiones", by the reaction of certain olefins and mercaptans with sulphur under severe conditions[94,95]:



α-Dithiopyrone was also obtained from α-pyrone by successive treatment with phosphorus pentasulphide and sodium hydrogen sulphide[93]. Treatment of α-dithiopyrone with alkali leads to α-thiopyrone[93], which was also obtained by the reaction of α-pyrone with potassium hydrogen sulphide[96]:



The aromatic character of α-thio- and α-dithio-pyrones is indicated primarily by their unusual thermal stability. When α-thiopyrone is brominated, substitution and not addition takes place[92].

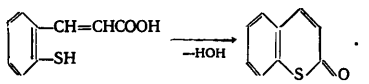
α-Thiopyrone is soluble in water, which means that it is a polar compound. Since it is a pseudotropone, its physical and chemical properties are best represented by the formula:



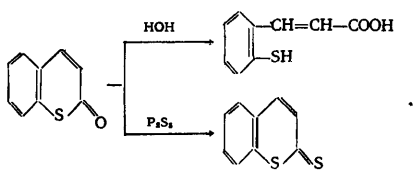
However, α-thiopyrone cannot be oxidised to the corresponding pseudotropolone, because the attack of oxidising agents is directed primarily to the divalent sulphur. On formation of the sulphone, the free electron pair of the sulphur atom is removed from the conjugation with the ring, as a result of which the compound loses its aromatic character[97].

Unsaturated δ-Thiolactones Condensed with a Benzene Ring

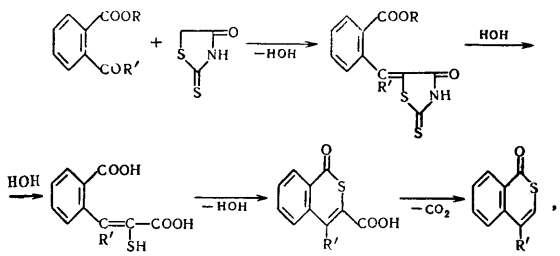
These compounds are not aromatic. One of such thiolactones, thiocoumarin, is formed on lactonisation of *o*-mercaptocinnamic acid[98]:



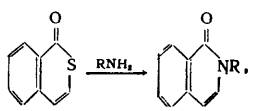
The *cis*-acid lactonises spontaneously, but the lactonisation of the *trans*-acid requires heating with dehydrating agents. The preparation of thiocoumarin from coumarin on heating with various derivatives of thiocarbonic acid [CS_2, $CS(NH_2)_2$, etc.] has been described[15]. Alkaline hydrolysis of thiocoumarin yields *cis*-*o*-mercaptocinnamic acid[98], and its reaction with phosphorus pentasulphide gives dithiocoumarin[99]:



The δ-thiolactone isomer of thiocoumarin (1,2-dihydro--1-oxo-2-thianaphthalene) is formed on alkaline hydrolysis of the products of the condensation of *o*-acylbenzoic acid or its esters with rhodanine[100,101]:

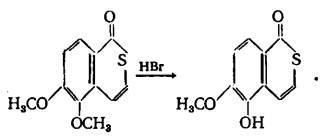


where R″ = H or CH_3. Ammonia and primary amines react with 1,2-dihydro-1-oxo-2-thianaphthalene with the formation of the corresponding isoquinoline derivative[101]:

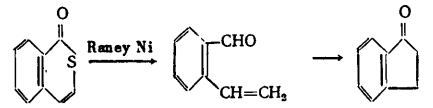


where R = H or alkyl. The mechanism of this reaction has not been studied.

1,2-Dihydro-5,6-dimethoxy-1-oxo-2-thianaphthalene dissolves in alkali on heating, but the hydrolysis product has not been investigated. Boiling hydrobromic acid does not affect the ring, causing only the demethylation of the 5-methoxy-group[101]:

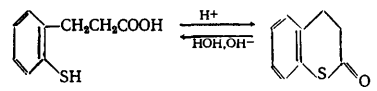


Elimination of sulphur from 1,2-dihydro-1-oxo-2-thianaphthalene with Raney nickel yields 1-indanone with the intermediate formation of *o*-formylstyrene[102], which is known to isomerise to 1-indanone:

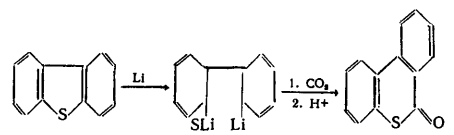


Saturated δ-Thiolactones Condensed with Benzene Rings

Lactonisation of *o*-mercaptohydrocinnamic acid gave dihydrothiocoumarin, which on alkaline hydrolysis was reconverted into the initial acid[98]:



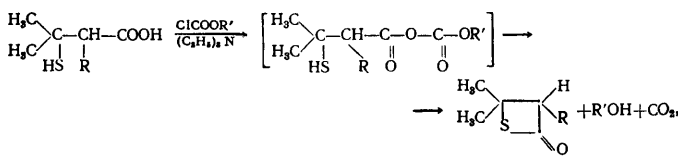
3,4-Benzothiocoumarin, a δ-thiolactone condensed with two benzene rings, was obtained by splitting dibenzothiophen with lithium and subsequent carboxylation[103]:



3,4-Benzocoumarin is obtained from dibenzofuran under the same conditions.

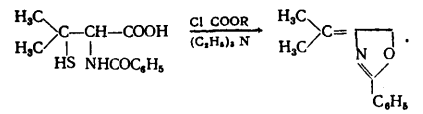
4. β-THIOLACTONES

β-Thiolactones have been less thoroughly investigated than γ- and δ-thiolactones. Attempts to prepare four--membered thiolactones were made in 1948 by Süs[104], but the first representatives of the class of β-thiolactones were actually obtained by Knunyants and coworkers in 1955[105,106] by the anhydridisation of β-mercapto-acids with chloroformic ester in the presence of triethylamine:



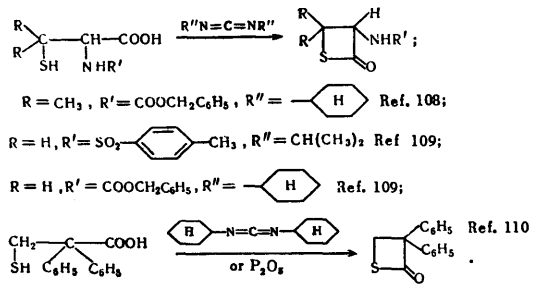
where R = H, $NHCOCH_3$, $NHCOCH_2C_6H_5$, or $NHCOCH_2$. .$NHCOCH_2C_6H_5$.

Anhydride formation from *N*-benzoyl-ββ-dimethylcysteine gave an unsaturated oxazolone:



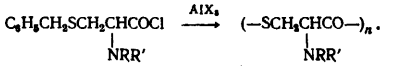
However, in the case of other α-acylamino-β-mercapto--acids the formation of oxazolone, even as a side-product, is not observed, the sole reaction products being β-thiolactones, as mentioned above. Thus anhydride formation from *N*-acyl-ββ-dimethylcysteine derivatives with chloroformic ester does not as a rule give the five-membered ring of oxazolone, the four-membered ring of β-thiolactone being formed[106,107].

Carbodiimides and phosphorus pentoxide can also be used as dehydrating agents in the preparation of β-thiolactones from β-mercapto-acids:

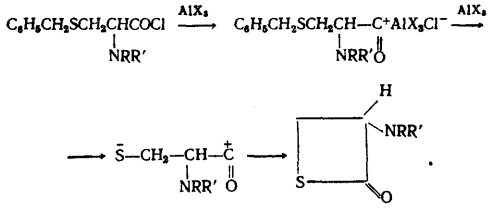


The dehydration of β-hydroxy-acids does not as a rule yield β-lactones.

Fleš and coworkers [47,111] obtained α-acylamino-β-propiothiolactones from the acid chlorides of *N*-acyl-*S*-benzylcysteine derivatives by the action of aluminium chloride or bromide. This method is similar to that used for the preparation of thio-oxindole from *o*-methylthiophenylacetyl chloride (p. 500), and its application is restricted to β-thiolactones which do not contain substituents sensitive to the action of aluminium chloride and the hydrogen chloride liberated during the reaction. The preparation of β-thiolactones by Fleš' method requires two moles of aluminium halide per mole of the initial acid chloride. When the acid chloride of an *N*-acyl-*S*-benzylcysteine derivative is acted upon by one mole of AlX_3, a linear polythioester is formed:

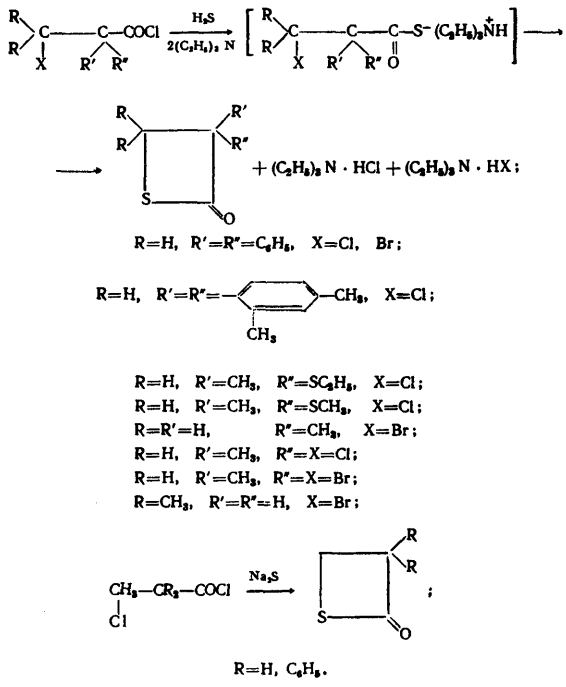


Ingold proposed the following mechanism to account for the different behaviour of the acid chlorides of *N*-acyl-*S*-benzylcysteine derivatives in the presence of one and two moles of aluminium halide [47]:



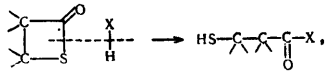
The first mole of AlX_3 ionises the covalent bond between the chlorine and the acyl group. Because of steric hindrance, the resulting cation is incapable of undergoing intramolecular debenzylation, but it can debenzylate another similar cation or molecule, which results in the formation of a polythioester. The second mole of AlX_3 debenzylates the acylium cation with the formation of a betain structure in which the reaction centres with opposed charges readily approach each other and the four-membered ring of β-thiolactone is formed.

The simplest and most convenient method for the preparation of β-thiolactones consists in the reaction between the acid chlorides of β-halogenocarboxylic acids with hydrogen sulphide in the presence of triethylamine [110] or a metal sulphide [30,31,110]:



The yields of β-thiolactones are related to their stability, which depends on the nature of the substituents. As in the case of γ- and δ-thiolactones, the stability of the β-thiolactone ring increases with the number of substituents.

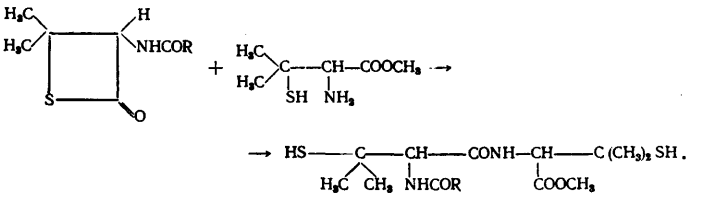
β-Thiolactones readily react with various nucleophilic reagents, the β-thiolactone ring always being ruptured at the S–acyl bond:



where X = OH, OR, or NRR'.

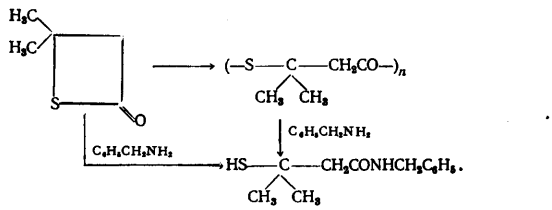
The hydrolysis of β-thiolactones in the presence of acids and alkalis leads to β-mercapto-acids, while their alcoholysis in the presence of acids or alkoxides gives esters of β-mercapto-acids. Ammonia [112] and aromatic [105,106,113] and aliphatic [105,112,113] amines split β-thiolactones with the formation of β-mercapto-acid amides.

The splitting of α-acylamino-β-thiolactones with α-amino-acids [113], their salts [105,112], and esters [114] can be used for the synthesis of peptides, for example:

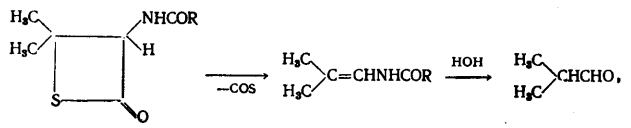


Knunyants and coworkers [114] were the first to achieve peptide synthesis using β-thiolactones. Later, this method was employed by Sheehan [108] and Fleš [109,111], and other workers extended it to γ-thiolactones (see p. 496).

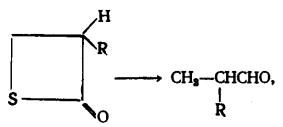
β-Thiolactones readily polymerise[105,111,113], the resulting polythioesters behaving as acylating agents[111,115], like the cyclic monomers, for example:



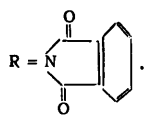
Other reactions which have been described, in addition to those between β-thiolactones with nucleophilic reagents and polymerisation, are pyrolysis of α-phenylaceturoylamino-ββ-dimethyl-β-propiothiolactone with elimination of carbon oxysulphide[106]:



where R = $CH_2NHCOCH_2C_6H_5$, and the reductive elimination of sulphur from α-phthalimido-β-propiothiolactone with Raney nickel[47]:



where

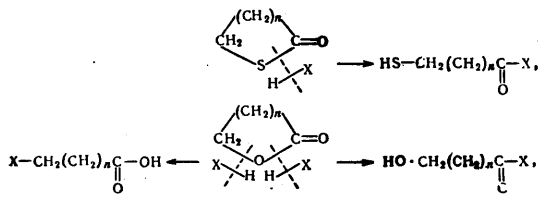


Treatment of α-benzyloxycarbonylamino-ββ-dimethyl--β-propiothiolactone with HBr in acetic acid did not result in ring opening. Under these conditions Sheehan[108] obtained the hydrobromide of α-amino-ββ-dimethyl-β-propiothiolactone.

β-Thiolactones are formed more readily and undergo ring rupture with greater difficulty than their oxygen analogues — β-lactones. This distinguishes β-thiolactones from γ- and δ-thiolactones, which are formed with greater difficulty and undergo ring rupture more readily than γ- and δ-lactones. The esters of carbothiolic acids are also less readily obtainable and more reactive than their oxygen analogues — carboxylic acid esters. Thus among the compounds with the $-\overset{\overset{O}{\|}}{C}-S-$ grouping only β-thiolactones are more stable than their oxygen analogue with the grouping $-\overset{\overset{O}{\|}}{C}-O-$. Apparently, this is due to the β-thiolactone ring being less strained than that of β-lactone, because the valence angle of sulphur is close to 90°¶. In γ- and δ-thiolactones and thiolic acid esters the decisive factor is the lower stability of the $\gtrless C-S$ bond compared with $\gtrless C-O$.

¶ From spectroscopic data, Fleš[111] confirmed that the four-membered ring in β-thiolactones is less strained than in β-lactones.

Thiolactones with rings of different sizes differ from the corresponding lactones not only in the stability of the ring but also in the nature of their reactivity. β-, γ-, and δ-thiolactones are split by nucleophilic reagents only at the S-acyl bond, whereas their oxygen analogues are split by the same agents at either the O-acyl or O-alkyl bonds.



where n = 1, 2, or 3.

Thus thiolactones behave only as acylating agents, in contrast to lactones which have both acylating and alkylating activity. The esters of carbothiolic acids are also more active acylating agents than carboxylic acid esters.

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Institute of Organoelemental Compounds, USSR Academy of Sciences