Review on Synthesis and Structural Characterization of 3-Acyltetronic Acids and 3-Acylthiotetronic Acids
First Candidate Module Report

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June, the 14\textsuperscript{th} 2005
Preface

Trying to make efforts in organic chemistry can of course be a hard challenge. But to experience success in organic synthesis and to discover the properties of the new born babies pays off the industrious chemist. The same spirit must have driven the researchers since the beginning of the last century to make efforts towards the synthesis of 3-acyltetronic and 3-acylthiotetronic acids, respectively. Today, there exist several methods for the synthesis of 3-acyl(thio)tetronic acids and derivatives of biological interest. But nevertheless, no simple, high-yielding universal method has been published, which is capable of producing acylated tetronic acids in an industrial scale. So, the method has still to be found.

The distinguished principle of tautomerism and the impact of hydrogen-bonding on the properties of innumerable compounds made the employment with these topics very important. The discussion of this field with respect to acyl(thio)-tetronic acids has sometimes been controversial. Therefore, it seems to be necessary to summarize the results of the past decades. Exactly for that reason, the authors of this essay are very pleased to guide the reader through the history of the chemistry of 3-acyltetronic, as well as 3-acylthiotetronic acids.
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Part I

Introduction
Chapter 1

Aims of this Thesis

The present essay on the syntheses and structural characterisation of 3-acyl tetronic and 3-acylthiotetronic acids, respectively, has the aim to summarize the literature results from the beginning of the tetronic acid’s chemistry to nowadays modern and sophisticated procedures and applications. To emphasize the importance of tetronic acid derivatives and their versatile application possibilities, an outline of the natural occurrence and biological activities is given as the very first part of the introduction. Furthermore, the basic principles of the chemistry of β-dicarbonyl compounds are sketched out briefly to construct the fundamentals for the further discussions. In this regard, the concepts of tautomerism and resonance-assisted hydrogen-bonding are presented, as well as common reactions of these substances.

In the main part the spectroscopical methods to determine the structure of 3-acyltetronic and 3-acylthiotetronic acids are described and the results are discussed. Beginning with the most important technique - the nuclear magnetic resonance spectroscopy on different nuclei - the outcomes of the common spectroscopical methods will be illustrated to give an entire picture of the structural features. Concerning this point, IR-, Raman- and UV/vis-spectroscopy and crystallographic methods like X-ray diffraction and neutron scattering will be mentioned, too.

The second major section focuses on the syntheses of 3-acyl(thio)tetronic acids. The purpose of the authors was to give a summary as complete as possible, in which most of all different protocols are presented. These will be critically examined on their overall yields, the straightforwardness and the availability of
the starting materials as well. Finally, this report should be a part of the historical and theoretical backbone of the corresponding second candidate module reports.
Chapter 2

Natural Products and Biological Activities

3-Acyltetronic acids and 3-acylthiotetronic acids show an extensive and various presence in nature. Therefore, it is not astonishing, that their derivatives find several significant applications in medicine. These aspects are subsequently presented.

2.1 Derivatives of 3-Acyltetronic Acids

One of the most important tetronic acids is ascorbic acid [1] (Fig. 2.1).

![Ascorbic Acid](image)

Figure 2.1: Ascorbic Acid

This as vitamin C known compound is found in humans, animals and almost all plants. It is essential for wound healing and the immune system and is used as an antioxidant for food technical purposes.

Moreover, tetronic acid derivatives have been found in moulds as fungal metabolites [2, 3]. This discovery was decisive for medicinal applications as antibiotics. If the mould *Penicillium Charlesii* is grown on glucose, five closely related acids of the tetronic acid type are produced (Fig. 2.2).
Investigations of natural products from marine sources have provided another kind of metabolites, 4-ylidenetetronic acids, which were extracted from marine sponges [1]. These compounds, which additionally contain furan ring systems, also possess strong antibiotic activity. One important example, variabilin, is shown in Fig. 2.3.

Early Eskimos used lichens to poison wolves, but it was not known until 1952, that the toxicity is generated by pulvinic acids [1] (Fig. 2.4). In the following years, a number of those analogous have been synthesized and many show useful anti-inflammatory properties. This group also features a 4-ylidenetetronic ring system and is found in yellow and red pigments of lichens, as well as in pigments of mushrooms. However, their production is only possible in the presence of a fungal partner.
Further antibiotics have been isolated from the microbial species *Amycolatosis orientalis* No. Q427-8 [4](Fig. 2.5). This group of antibiotics possesses an antiviral effect and represents an unique macrocarbocyclic ring, which contains four tetronic acid moieties as 3-acyltetronate groups. By the $^{13}$C-NMR spectrum was found out, that a symmetrical, dimeric structure is given.

![Diagram of Antiviral Antibiotics](image)

Figure 2.5: Antiviral Antibiotics

Other in nature appearing products are 3-alkanoyl-5-hydroxymethyltetronic acids (Fig. 2.6), which have inhibitory activity against HIV protease [5]. Six homologues of this group with a side chain up to 14 carbon atoms have been isolated as sodium salts from a bacteria strain.

One of them [R=(CH$_2$)$_{14}$CH$_3$] is a specific inhibitor of protein tyrosine phosphatases [6, 7]. Reversible phosphorylation of proteins is a fundamental mechanism of signal transduction. Disorders in these phosphatases cause several serious diseases such as cancers or diabetes. Therefore, the characterisation of them is an important focus in biological research to find candidates for therapeutics.
3-Acyltetronic acids also appear as intermediates in synthesizing prostaglandin analogs [8]. Prostaglandins are important bioregulators, which participate in a large number of biochemical reactions and are capable of influencing cell metabolisms. However, a way of obtaining synthetic analogs had to be found, because their concentration in natural materials is very low and due to their instability from the chemical and metabolic point of view [9]. By that, 3-Acyltetronic acids, with a structure shown in Fig. 2.7, play an important role.

2.2 Derivatives of 3-Acylthiotetronic Acids

Although the derivatives of thiotetronic acids have not such a wide range in biological activity, they possess a worth mentioning importance.

3-Acetyl-5-(4-fluorobenzylidene)thiotetronic acid (Fig. 2.8) exhibits a potent activity against a veterinary respiratory pathogen [10]. Moreover, it prevents the development of wound inflammation, as well as allergic reactions in experiments with rats [11].

The most important one, which has no acyl group at position 3, is the antibiotic thiolactomycin (Fig. 2.9), which was isolated from a soil bacterium [12] and is present as the (5R)-enantiomer. It is an unique thiolactone, that has been shown to exhibit anti-arthritis and, especially, anti-mycobacterial activity by inhibiting of fatty acid biosynthesis as building blocks for the biosynthesis of membrane
2.2. DERIVATIVES OF 3-ACYLTHIOTETRONIC ACIDS

phospholipids [13]. Referring to this, it is used as a potent anti-tuberculosis agent, that prevents the growth of the cell membranes of those harmful bacteria.

All in all, thiolactomycin shows moderate activity against a number of pathogenic bacteria and minimizes the resistance to human therapeutics [10].
Chapter 3

The Chemistry of $\beta$-Dicarbonyl Compounds

3.1 Tautomerism

In general, $\beta$-dicarbonyl compounds could exist in several conformationally different tautomeric forms, which could be in equilibrium. Fig. 3.1 shows possible conformers of a $\beta$-diketone, assuming planarity of the carbon and oxygen framework. Which conformation is favoured depends strongly on the chemical structure of the substance.

Three types of proton transfer reactions are feasible in $\beta$-diketone systems:

- relatively slow exchange between the vinylic and the enolic protons (i.e. the keto $\rightleftharpoons$ enol tautomerism)

- rapid intermolecular exchange of protons between OH groups on different molecules, fast on the NMR time-scale

- extremely fast intramolecular proton exchange observed in cis enols (corresponding to an oscillation between the two minima of the potential energy well of the OHO hydrogen-bond)

In principle the tautomeric composition of a $\beta$-dicarbonyl system is expressed as the molar percentage of the enol tautomer at equilibrium. This equilibrium is influenced by several factors:

- solvent
CHAPTER 3. THE CHEMISTRY OF $\beta$-DICARBONYL COMPOUNDS

Figure 3.1: Conformations of a $\beta$-Diketone [14]

* distinguishable by extra conformers in asymmetric $\beta$-diketones or symmetric $\beta$-thioxoketones
3.1. TAUTOMERISM

- temperature
- presence of other molecules, that are capable of forming hydrogen-bonds
- $\alpha$-substituents
- $\beta$-substituents.

Based on a review of J. Emsley, the particular influences are discussed [14]. At first, the solvent effects should be mentioned. It could be stated, that the lower the polarity of the solvent, the higher the percentage of the enol tautomer. There is an almost inverse linear relationship between the permittivity $\epsilon$ of the solvent and the ratio of the enol tautomer. Another effect is the capability of the solvent to act as a hydrogen-bond acceptor or donor. Hydrogen-bond donors interact better with the keto tautomer, while acceptors may possibly compete for the enol proton’s attention.

The effect of temperature variation is correlated to the enthalpy and entropy of enolisolation. A temperature increase leads to a decrease of the percentage of the enol tautomer. The present data in 1984 was rather scarce. In order to study the influence of the presence of other dissolved species fluoride, water and triethyl amine, respectively, were added to solutions of acetylacetone (AcAc). The effect of fluoride turned out to be remarkable. The AcAc was entirely transferred into its enolic form, even when the AcAc:fluoride ratio was 50:1 (for AcAc in acetonitrile added K(crown)F or n-Bu$_4$NF). This dramatic change may be owing to a very asymmetric hydrogen-bond formed after proton transfer to the fluoride. The addition of water to a benzenic solution of AcAc also increased the amount of the enol tautomer due to an 1:1 association of water to AcAc. The effect of triethyl amine is quite similar and results also in an increase of the percentage of the enol form.

Now, the focus should be centred on substitution effects of both $\alpha$- and $\beta$-substitution. It has been found, that sterically demanding $\alpha$-substituents lead to a decrease of the enolic form of AcAc. For example, an iso-propyl or sec-butyl group as $\alpha$-substituent depresses the amount of the enol almost to zero. The presence of a bulky $\alpha$-group might be expected to force the carbonyl oxygens closer together and to strengthen in this way the hydrogen-bond. But the interaction of this groups with $\beta$-substituents has also to be taken into account. The only way to get rid of these difficulties is to adopt a diketo conformation (cis or trans).
The effect of the space consumption of a β-substituent varies on its nature. The relationship was not clarified by Emsley. A β-diketone bearing electron withdrawing groups favours the enol tautomer. It was also observed, that groups, which could enhance the delocalization in the enol ring, force the system to a more symmetrical hydrogen-bond. But anyway, this influence should be furtherly discussed in the next section.

### 3.2 Resonance-Assisted Hydrogen Bonding

Emsley reviewed the accounts of research on strongly hydrogen-bonded systems in 1980 [15]. He summarized the criteria to distinguish between weak and strong hydrogen-bonding. In this regard, he reported, that the O-H stretching vibration frequency is lowered and the chemical shift for the hydrogen-bonded proton is shifted more downfield for a stronger hydrogen-bond. In 1984, he reviewed the research on β-diketones with the aim to give a status-quo report [14]. Consequently, the hydrogen-bonding of cis enol tautomers of β-diketones is strong. The bond energy is in the range between 12 and 24 kcal/mol and the contact distance $d_{O-O}$ can be settled in the region around 2.45-2.55 Å. The proton is situated, depending on β-substitution, in a double well potential. Proton tunneling should be possible due to a low activation barrier in comparison to the zero-point-vibrational-energy. The barrier height corresponds to $d_{O-O}$.

Gilli and coworkers observed during a X-ray and neutron crystallographic investigation on the β-diketone fragment containing compounds a strong correlation between the strength of the hydrogen-bond and the delocalization in the system [16]. This effect can be explained qualitatively by means of a synergism between hydrogen-bonding and resonance and was therefore called resonance-assisted hydrogen-bonding (RAHB). According to their 1989’s publication, the basic principles will be outlined in this section.

The hydrogen-bond formed in such a system acts as a balance between several energy values:

- $E_{HB} = \text{energy of the hydrogen-bond}$
- $E_{RES} = \text{resonance energy of the } \pi\text{-system}$
- $E_{BP} = \text{bond polarisation energy to dissociate partial charges on the oxygens}$
3.2. RESONANCE-ASSISTED HYDROGEN BONDING

In order to minimize the total sum of these energy contributions, electron density will be transferred from the left oxygen of Fig. 3.2 to the right. This electron shift is connected with a creation of partial charges on both oxygen atoms, which leads automatically to a Coulomb-Attraction of the involved oxygens accompanied by a shortening of $d_{O-O}$, and an elongation of the O-H-bond. In this regard, the proton movement corresponds to a vacancy going to the right or a negative charge going to the left oxygen. The building up of partial charges on the oxygen atom is feedbacked by the movement of the proton trying to compensate the charge separation. Finally, the hydrogen-bond will be strengthened by this mechanism, which is stronger than in non-resonant hydrogen-bonded systems. A slightly different interpretation of the RAHB-effect was given by Staley et al. [17]. Owing to $\pi$-orbital interactions the hydrogen-bond should be strengthened. The hydrogen-bond is formed by electron donation from the in-plane lone pair of the carbonyl oxygen in Fig. 3.2. Resonance involves the out-of-plane lone pair on the enol-oxygen to donate electron density to the right oxygen. So, the basis energy of the right one is increased owing to a decreased electronegativity. Thus, the carbonyl oxygen gets a better electron donor, as well as a stronger hydrogen-bond acceptor.

Gilli also provided a semiempirical calculation method for a quantitative estimation of the total hydrogen-bond energy. They obtained values of around 4.8 kcal/mol for ice and 12.8 kcal/mol for acetylacetone corresponding well to the $ab\ initio$ and experimental values, respectively, and showing, that the hydrogen-bond energy in a RAHB system is some three times bigger than in not-delocalized
systems (e.g. ice). Furthermore, the model fits to the results found by means of IR-, NMR- and gas-phase-electron-diffraction studies showing its reliability.

The great advantage of the RAHB-concept is its generality. The results found for enolone systems like acetylacetone can be transferred to common heterodiene and other heteroconjugated systems (i.e. enaminoes, enamo-imines, enol-imines and coupling of DNA-bases, namely thymine-adenine and cytosine-guanine).

In a more recent paper [18] Gilli et al. examined the influence of the 1,3-substitution on the strength of the intermolecular hydrogen-bond by crystal structure determinations using 1,3-diaryl-1,3-propandiones as model compounds. It turned out, that the favoured structure will be the one, for which resonance can generate the larger negative or positive charges on the carbonyl or hydroxyl oxygens, respectively. Since this particular charge distribution furnishes the stronger intramolecular hydrogen-bond.

Gilli also focussed on intermolecular association of β-diketone enols via resonance-assisted hydrogen-bonds. [19]. Resonant β-chains predominate over other crystal packings in the crystal structures of these compounds. The feature of remarkably short O-O contact distances could be observed upon the formation of resonant β-chains as well. This proves, that the RAHB-principle describes also intermolecular associates.

### 3.3 Common Reactions and Synthetic Applications

In this section the basics of the preparation and the synthetic applications of β-dicarbonyl compounds are outlined. The biggest part of the synthetic versatility of β-keto carbonyl compounds arises from the acidity of the α-proton. Thus, a lot of these reaction schemes could be transferred to β,β′-tricarbonyl compounds like 3-acyltetronic acids.
3.3. COMMON REACTIONS AND SYNTHETIC APPLICATIONS

Syntheses [20, 21]

**Claisen-Condensation**  A very general reaction of esters is the self-condensation reaction after the treatment with a base. This reactivity is due to the acidity of the $\alpha$-proton(s). In the first step the esterolate-anion is obtained by treatment of the ester with a base (i.e. sodium alkoxide). Afterwards, the enolate reacts in an addition-elimination reaction with the carbonyl-group of another ester molecule to give a 3-ketoester. This is deprotonated by the base to drive the equilibrium towards the product. Finally, the product is set free by an acidic work-up.

![Figure 3.3: Claisen Ester-Condensation](image)

The intramolecular variation of the Claisen-Condensation is called Dieckmann-Cyclisation yielding lactones. To obtain 3-diketones the Claisen-Condensation can be applied to ketones. In this case the ketone is deprotonated and then added to an ester.

**Acylation of Alcohols with Diketene**  The industrial way to acetoacetic ester is via the acylation of ethanol by diketene (cf. Fig. 3.4). The reaction takes place without any base or acid as catalyzt. The high reactivity of diketene is due to its four-membered ring structure. The lactone-oxygen is not able to stabilize the carbonyl-group like in open-chained esters because of the relatively high ring-strain. Furthermore, the tetrahedral intermediate of the reaction causes rehybridisation of the carbonyl carbon from $sp^2$ to $sp^3$, which reduces the Bayer-Strain of the lactone.

The use of diketene restricts the 3-ketoester syntheses to acetyl-derivatives. Acyl-Meldrum’s acid as a synthetic equivalent of diketene overcomes this problem.
Acylation of Alcohols with Acyl-Meldrum’s Acids  In the same way as the reaction mentioned above acylated Meldrum’s acids react with alcohols to β-ketoesters without a catalyzt [22]. Meldrum’s acid itself is destabilized by dipol-dipol interaction due to its s-trans conformation. The transition to a tetrahedral intermediate as it is observed in the alcoholysis reaction reduces this interaction. Moreover, the oxy-anion of the intermediate structure can be stabilized by hydrogen-bonding from the neighbouring enolic proton. The addition of the alcohol is followed by an abstraction of acetone and a decarboxylation of the β-ketoacid (Fig. 3.5) to the desired ester.

By varying the acyl-Meldrum’s Acid many different β-ketoester are accessible.

Common Reactions

Alkylation of Enolates  Once that an anion of a β-dicarbonyl compound is prepared it acts as a nucleophile. The treatment with any alkylation reagents such as alkyl halogenides leads to alkylated species. In figure 3.6 are some examples.

Decarboxylation of 3-Ketoacids  A synthetically useful property of β-ketoacids is the decarboxylation upon heating. The concerted reaction’s transition state is a six-membered ring resembling to that of an ester pyrolysis (cf. Fig. 3.7).

Acetoacetic-Ester-Syntheses  The reaction sequence alkylation → ester hydrolysis → decarboxylation of acetoacetic ester derivatives - commonly known
3.3. COMMON REACTIONS AND SYNTHETIC APPLICATIONS

Figure 3.5: Acylation of Alcohols by Acyl-Meldrum’s Acids

Figure 3.6: Alkylation of 3-Oxocarbonyl Compounds via Enolates

Figure 3.7: Decarboxylation of a β-Ketocarboxylic Acid
as a acetoacetic-ester-synthesis - leads to 3-substituted or 3,3-disubstituted methyl ketones.

**Malonic-Ester-Syntheses** Closely related to the acetoacetic-ester-syntheses are the malonic-ester-syntheses. Starting with malonic ester, which can be alkylated in the common way - within the boundaries of regular $\text{SN}_2$-reactions - an alkylated ester is obtained. Following the upper-mentioned sequence, the hydrolysis leads to a $\beta$-dicarboxylic acid, which is subsequently decarboxylated by heating. This reaction sequence yields 2-substituted or 2,2-disubstituted carboxylic acids.

![Figure 3.8: Malonic-Ester-Synthesis of 2-Methyldecanoic Acid](image)

**Knoevenagel-Condensation** The prototype of a Knoevenagel-Reaction is the condensation of an aldehyde or a ketone to a malonic ester to give a $\alpha,\beta$-unsaturated carboxylic acid ester. In general, the reaction is possible with a lot of active methylene compounds. As a basic catalyst piperidine or even piperidiniumacetate can be used, for the basicity of the acetate ion is high enough to produce a sufficient equilibrium amount of piperidinium enolate.

So, this reaction can be seen as a sequence of a hydroxyalkylation of an enolate followed by a E1cb-elimination (Fig. 3.9) and thus, is related to the Aldol-Condensation.

**Michael-Addition** The 1,4-addition of an enolate produced from a $\beta$-dicarbonyl compound with a $\alpha,\beta$-unsaturated carbonyl compound is commonly known as a Michael-addition (cf. Fig. 3.10). Popular Michael-acceptors are $\alpha,\beta$-unsaturated ketones (e.g. methylvinylketone, MVK), aldehydes, nitriles or carboxylic acids. The reaction is catalyzed by a base like sodium ethanolate.

The Michael-Reaction followed by an intramolecular Aldol-Condensation is called a Robinson-Annulation.
3.3. COMMON REACTIONS AND SYNTHETIC APPLICATIONS

Figure 3.9: Knoevenagel-Condensation of a Carbonyl Compound to an Active Methylene Compound (EWG = Electron Withdrawing Group)

Figure 3.10: Michael-Addition of MVK to Diethyl Malonate
**Japp-Klingemann-Reaction**  In the sense of the upper mentioned reactions, the scheme presented here is an Azo-Coupling of an aromatic diazonium-salt with a $\beta$-dicarbonyl compound to give arylhydrazones. In general, the reaction is carried out under basic conditions in aqueous solutions. The anion of the 3-oxocarbonyl compound is built, which then reacts with the diazonium ion to an arylhydrazone. However, arylhydrazones with two electron withdrawing groups are unstable under these reaction conditions. They solvolyse to the resonance-stabilized anion and are then transferred to the arylhydrazon by an acidic work-up (cf. Fig. 3.11).

![Figure 3.11: Japp-Klingemann-Reaction](image-url)

Arylhydrazones are important starting materials for the Fischer-Indole-Syntheses.

**Tafel-Rearrangement**  A synthetically less important reaction is the Tafel-Rearrangement, which occurs as a by-reaction upon electrolytical reduction of substituted acetoacetic ester derivatives in ethanolic sulphuric acid on a lead
cathode.

Figure 3.12: Tafel-Rearrangement occurring during Cathodic Reduction
In general, the sulphur atom has a relatively large atomic diameter compared with other atoms involved in organic compounds, e.g. oxygen. This causes changes in organic molecules when oxygen is substituted by a sulphur atom. In contrast to β-ketoesters, β-thiooxoketones exhibit a lower intramolecular hydrogen-bonding [23], because the approach of the larger sulphur atom to the neighboured carbonyl group is more hindered by geometric effects. Considering the 3-acyltetronic acids, a substitution of an oxygen by a sulphur atom effects longer bonding distances to the next carbon atom and therefore, higher ring strain. Hence, these sulphur compounds are higher in energy than the oxo cases. Consequently, this facts cause different behaviours in chemical reactivity, as well as differences in spectroscopic studies.
Part II

Synthesis and Structural Characterisation of
3-Acyltetronic and
3-Acylthiotetronic Acids
Chapter 5

Structure of 3-Acyl(thio)tetronic Acids

5.1 Introduction

Since the early sixties it is known, that intramolecular hydrogen bonds in enols of \( \beta \)-di- and particularly \( \beta, \beta' \)-tricarbonyl compounds are very strong. By NMR and IR investigations of hydrogen-bonding and tautomerism in cyclopentanone enols Forsén found out, that the dicarbonyl compounds are only partly enolized, whereas the tricarbonyl compounds are all completely enolized [24]. Three years later it was shown by the same author, that 2-acetylcyclopentane-1,3-diones can occur in several enolic forms (Fig. 5.1) [25]. The equilibria \( a \Leftrightarrow b \) and \( c \Leftrightarrow d \) represent the "internal" tautomers; \( a, b \Leftrightarrow c, d \) the "external" tautomers. The "internal" tautomers are generally interconverted very fast, so that they show signals with average chemical shifts. The "external" tautomers often give separate NMR signals, especially in unsymmetrical \( \beta, \beta' \)-triketones like 3-acyltetronic acids, which contain an oxygen atom in the ring system. Consequently, it was obvious to start spectroscopic examinations also on 3-acyltetronic acids and 3-acylthiotetronic acids, respectively, also with regard to the dependence of solvents and temperature. The results of the determined spectroscopic properties since this time are subsequently summarized.
5.2 Nuclear Magnetic Resonance Spectroscopy

5.2.1 $^1$H-NMR Spectroscopy

In 1976, the first publications concerning $^1$H-NMR spectroscopic studies on tetrionic acid analogs have appeared. Yamaguchi et al. also suggested "external" and "internal" tautomeric structures for 3-acetyl tetrionic acid and 3-acetylthiotetronic acid [26] like Forsén in 1967 for 2-acetylcyclopentane-1,3-diones (Fig. 5.2) [25].

They observed, that the methylene, as well as the methyl protons are splitted into two singlets. They explained the splitting of the methylene protons around 5 ppm (cf. Fig. 5.3) due to the diamagnetic anisotropic effect of the ring carbonyl group (position 4) on these neighbouring protons, which is more dominant for the $c$- and $d$-forms than for the $a$- and $b$-forms. The effect of the enolized carbonyl group (a) or hydrogen-bonded carbonyl group (b) is more negligible, so that the signal at lower field was assigned to the pair of the $c$- and $d$-forms.

The splitting of the NMR signals by the "internal" tautomers should not be detectable because of their very fast interconversion. However, they claimed, that the internal tautomers of these compounds exchange rather slowly, slow enough to be detected by NMR measurements at 90 MHz. They interpreted, that the
5.2. NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

X = O, S

Figure 5.2: Tautomeric Structures of 3-Acetyl(thio)tetronic Acids

Figure 5.3: $^1$H-NMR Spectrum of 3-Acetyl(tetronic Acid in CDCl$_3$ [26]
methyl protons (signals at 2.3-2.6 ppm) of the \(a\) - and \(c\) - forms are influenced by the diamagnetic anisotropic effect of the two carbonyl groups, the ring carbonyl (position 2 or 4), and the acetyl carbonyl group, whereas the methyl protons of the \(b\) - and \(d\) - forms are influenced only by one ring carbonyl group (position 2 or 4). Therefore, the signal at lower field was attributed to the pair of the \(a\) - and \(c\) - forms.

However, after this report, Yamaguchi et al. recognized, that this splitting is not due to their described theory, since the interconversion of the ”internal” tautomers is too fast to be detected on the NMR time scale, but it is given by the ”external” tautomers as well. Finally, they retracted their original interpretation three years later [27].

Chemical shifts of enolic protons are also used to estimate the strength of intramolecular hydrogen-bonding. A strong interaction causes a low-field shift for the enolic proton. This fact shows, that the intramolecular hydrogen-bonding of five-membered cyclic \(\beta,\beta'\)-triketones is weaker than of the acyclic analogs or six-membered cyclic triketones. The stronger contraction of five-membered ring systems effects, that the two oxygen atoms bridged by a hydrogen atom are located further apart from each other. They could exhibit, that 3-acetyltetronic acid (\(\delta=11.38\) ppm) and 3-acetyltetramic acid (Fig. 5.2, \(X=\text{NH}, \delta=11.42\) ppm) have a weaker intramolecular hydrogen-bonding than 3-acetylthiotetronic acid (\(\delta=16.10\) ppm), whose chemical shift is usual for acyclic \(\beta,\beta'\)-triketones and six-membered cyclic triketones.

Yamaguchi et al. also made spectroscopic studies on the tautomerism on the Schiff Bases of tenuazonic acid analogs (Fig. 5.4) [28]. These compounds also show splitted signals in the \(^1\text{H}-\text{NMR}\) spectra, which are assigned analogously to the 3-acetyltetronic acid analogs. The chemical shift for the exocyclic NH proton is found around 12 ppm in all cases. From the intensity ratios of the ring methylene signals they calculated the ratios of the external tautomers, with the result, that the \(a,b\) forms of tenuazonic acids dominate \((a,b/c,d=1.13)\), whereas in the tetronic acid and thiotetronic acid analogs the \(c,d\) - forms are preferred \((a,b/c,d =0.37\) and 0.34, respectively).

De Keukeleire et al. examined the enol tautomers of 3-(3-methylbutanoyl)tetronic acid. (Fig. 5.5) [29]. They explained the individual distinction of these tautomers in that way, that the proton at the \(\alpha\) - carbon atom with respect to the carbonyl group resonates at higher field compared to the corresponding atom.
next to the double bond. Also Gelin and Pollet agreed with them \[30\]. Double enolization, which would imply 2,4-dihydrofuran systems, does not occur due to the strong stabilization by hydrogen-bridges.

Gelin and Hartmann found out, that 3-acetyl-5-arylidenetetronic acids (Fig. 5.6) are present in only one enolic form, since one single singlet is visible for the vinylic proton \[31\]. However, it was not possible to estimate the configuration of these compounds.

Saito and Yamaguchi showed, with some exceptions, that 3-acetyltetronic acids and 3-acetylthiotetronic acids do not effect any splittings of the methyl and methylene signals in other solvents than chloroform-$d$ \[32\]. They suggested two reasons: One is the rapid tautomeric interconversion accelerated by a polar solvent. The other one is the shift of the tautomeric equilibria to one side as a
result of the solvation effect. The intensity of the methylene signal of the \( c,d \)-forms decreased, when DMSO-\( d_6 \) was added to a solution in chloroform-\( d \) and extinguished at a content of circa 25 % DMSO-\( d_6 \). Simultaneously, that of the \( a,b \)-forms was increased.

### 5.2.2 \( ^{13} \text{C}-\text{NMR} \) Spectroscopy

The \( ^{13} \text{C}-\text{NMR} \) spectra of 3-acyltetronic acids in deuteriochloroform also show two enolic forms. The spectra of 3-acyl-5-alkyltetronic acids (Fig. 5.7) feature the existence of two forms in different proportions [33].

The gate-decoupled spectra of 1a-1e show, that the C-5 carbon is attached to one hydrogen, whereas the C-3 carbon atom carries no hydrogen. Since the forms \( a,b \) and \( c,d \) in each equilibrium \( a \rightleftharpoons b \) and \( c \rightleftharpoons d \) are not distinguishable on the NMR time scale, the authors of this article suggested the nonexistence of these individual forms. They proposed, that these equilibria are describable by a structure of either the \( \alpha \)-type or the \( \beta \)-type as shown in Fig. 5.8.
The $^{13}$C-NMR spectrum of $1c$ has been investigated in the temperature range from -40 to 54 °C. Hence, they concluded, that the forms $a$, $b$, $c$ and $d$ are not present in this case. They extended their conclusion to the components $1a - 1f$, representing the $\alpha$- and $\beta$-form, respectively. Therefore, they claim, that this indicates the presence of only one potential minimum for the proton. They write, that the $\beta$-form in most cases is dominating in deuteriochloroform. Different substituents $R^1$ influence the ratio between the two forms and the value of the chemical shift of the C-6 carbon atom. Furthermore, it can be calculated, that the difference in values of C-6 between the two forms is independent of the nature of the substituents, what also suggests an identical structure of the two forms for all the components.

The $^{13}$C-NMR spectrum of $1c$ in deuteriomethanol shows only one set of signals, what can be explained by the fast interconversion between the $\alpha$- and $\beta$-form due to the exchange of the enolic hydrogen with the solvent.

$^{13}$C-NMR techniques are useful to observe the behaviour of carbon atoms involved in tautomerism. From this point of view, Saito and Yamaguchi made some further examinations on 3-acetyl tetronic acid analogs given in Fig. 5.2 [27]. They also observed the splitting of each signal by the ”external” tautomers and that
it is not possible to make the "internal" tautomers visible by lowering the temperature. The methyl (C-7), methylene (C-5) and olefinic (C-3) could be easily assigned to the corresponding signals by off-resonance decoupling measurements. The C-3 signals of these compounds appeared at 90-110 ppm, so that they were shifted to higher field compared with those of ordinary olefinic carbons, because of location at the \( \alpha \)-position to all three carbonyl groups in the molecule. The spectra were pretty complex and they had to assign the spectral features carefully; inductive and mesomeric effects have been taken into account. The signals of the hydrogen-bonded carbonyl groups shift to lower field compared with those of free carbonyl carbon atoms, whereas the enolized ones shift to higher field.

By long range \( ^{13} \text{C} \cdotp ^{1} \text{H} \) coupling measurements (gated-decoupling) they observed one pair of signals as a double doublet \( (^{2}J = 5.6-6.3 \text{ Hz}) \), which was assigned to C-6, and the other signals as triplets. It was also observed one larger long-range coupling \( (^{3}J = 1.9-3.0 \text{ Hz}) \) of C-2 with the methylene protons via the heteroatom. The assignment of each signal to one of the "internal" tautomers was furthermore made on the basis of calculated electron densities and of \( ^{1} \text{H} \)-NMR results. So, they explained the chemical shift of C-3 to higher field as mentioned above, that the lone-pair electrons of the oxygen atom in the chelate ring of the enol form can take part in \( \pi \)-conjugation, which increases the \( \pi \)-electron density on the olefinic carbon with the result to be more shielded. Moreover, the signals for C-2 of 3-acetylthiotetronic acid shift ca. 20 ppm to lower field compared with the other analogs. In the case of nitrogen and oxygen homologues, the charge density at C-2 is increased by the contribution of the electron-releasing mesomeric effect of the adjacent heteroatoms. For the sulphur homologues a reversed situation is present. Simultaneously, this atom resonates at lower field for the \( a,b \)-form than C-4 for the \( c,d \)-form in the sulphur compound, so that they concluded a double function of the sulphur atom, as \( \pi \)-electron acceptor and \( \delta \)-electron donor towards the neighbouring carbonyl group. The methylene carbon atoms appeared at higher field than those for the other homologues due to the higher electron density caused by the sulphur. All in all, the \( c,d \)-forms seem to dominate the structure of 3-acetyl tetronic acid and 3-acetylthiotetronic acid.

In DMSO-\( \text{d}_{6} \) solution, 3-acetyl-5-methyltetronic acid exhibits only seven peaks in the \( ^{13} \text{C} \)-NMR spectrum [30]. In the gate-decoupled spectrum two quartets around \( \delta = 190 \text{ ppm} \), which arose from the C-6 carbon atom. The signals at \( \delta = 200.32 \text{ ppm} \) and \( \delta = 195.47 \text{ ppm} \) were assigned to C-4, which is coupled with
5.2. NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

The H-5 proton as a doublet ($^2J=4$ Hz) and with the C-5 methyl group as a quartet ($^3J=2$ Hz). The C-2 signals at approximately $\delta=170$ ppm appear as a doublet ($^3J=2$ Hz).

Furthermore, Gelin et al. could show, that 3-acetyl-5-arylidenetetronic acids have only one set of sharp lines in deuteriochloroform, as they could previously establish by $^1$H-NMR spectroscopy. This time, they treated the problem of resolving the structure with regard to the dominance of the $a,b$- or $c,d$-forms by comparing the chemical shifts with those of similar compounds, but with inconsistent result.

Conclusively, $^{13}$C-NMR, as well as $^1$H-NMR measurements, gave the result, that 3-acyltetronic acid derivatives in deuteriochloroform show two sets of signals in their spectra. These splittings are effected by two "external" tautomeric forms. The "internal" tautomers have never been seen in the spectra, but it seems to be clear, that these compounds are 100 % enolized. The publications cited herein let assume, that the tautomeric equilibrium is predominated by the $c,d$-forms.

5.2.3 $^{17}$O-NMR Spectroscopy

Although there have been no publications concerning $^{17}$O-NMR measurements on tetronic acid derivatives or $\beta,\beta'$-tricarbonyl compounds, the method will be introduced at this point. Christ et al. published in 1961 a huge list of 127 substances they examined on their $^{17}$O-NMR spectra in order to systematize this at this time novel method [34]. Gorodetsky and coworkers attempted in 1967 the first studies of enol-enol tautomerism in $\beta$-diketones [35]. The natural isotopic distribution of oxygen is $^{16}$O : $^{17}$O : $^{18}$O = 99.757 : 0.038 : 0.205. Due to the low isotopic abundance of O-17 the substances had to be labelled. Totally $^{17}$O-labelled compounds were obtained by exchange with $^{17}$O-enriched water under acidic catalyzis. Specific labelled compounds were prepared from $^{17}$O-enriched monoketones.

The chemical shifts in $^{17}$O-NMR spectroscopy cover a range of 1000 ppm, which is divided into characteristic intervals correlated to the different functional groups containing the oxygen atom. The chemical shift for a hydroxylic oxygen is situated in the range of $\pm$ 40 ppm (relative to $H_2^{17}$O), while the carbonyl sp$^2$-hybridised oxygen can be found around -550 ppm. They were able to distinguish both tautomeric forms of asymmetric $\beta$-diketones. Two sets of resonance
peaks could be observed. A broad one in the region around -550 ppm, belonging
to the keto tautom, and two peaks in the range from 0 to -500 ppm corre-
sponding to the nonequivalent oxygens of the enol tautomer. From the chemical
shift of the enol peaks an equilibrium constant could be estimated in order to
determine the composition of the equilibrium mixture. Furthermore, they could
confirm the findings of Brown, Brewster and Shechter [36], who stated, that exo-
cyclic double-bonds stabilize five-membered rings and destabilize six-membered
ones due to the I-strain effect (cf. [37]). Thus, the equilibrium mixture of cy-
clohexanedione derivatives is predominated by the endo-cyclic double-bonded
tautomers and cyclopentadione compounds prefer the exo-cyclic configuration.
However, these measurements have not been done for acyltetronic acids, but in
principle the results should also match on this system.

5.3 Infrared Spectroscopy

The infrared absorption spectra of tetronic acid derivatives have been studied
since 1948. Trotter, Thompson and Wokes measured the IR absorption of hy-
droxytetronic acid, ascorbic acid and relatives as well [38] in order to distinguish
the substances in plant material by IR, since "traditional chemical" methods
failed. They also did first attempts to assign some of the spectral features. Hy-
droxytetronic acid has one intense band at approximately 1650 cm\(^{-1}\) belonging
to the C=C-stretching vibration. Another remarkable characteristic is a band
near 1750 cm\(^{-1}\), which was assigned to the C=O stretching mode of the lactone
group.

An important systematical investigation was carried out by Duncanson in
1953 [39], who measured the IR spectra of some tetronic acid derivatives in chlo-
roform solution and in the solid state. He focussed especially on the positions
of the carbonyl bands. With exception of \(\alpha\)-acetyltetronic acid, all specimens
(tetronic acid, \(\alpha\)-ethyl tetronic acid and \(\gamma\)-methyl tetronic acid) showed significa-
cantly lowered frequencies of the carbonyl bands in the solid state. This led to
the assumption, that these compounds strongly interact by means of hydrogen-
bonding in solids. Also the relatively low frequencies of the OH-stretching bands
support this assumption.

In the case of solid \(\alpha\)-acetyltetronic acid a strong band at 1758 cm\(^{-1}\), as-
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signed to the lactone-carbonyl group, has been observed. That points to, that the lactone-carbonyl group does not take part in intermolecular hydrogen-bond formation in the solid state. On dissolving tetronic acid and alkyltetronic acids in chloroform, the bands assigned to the double-bonds shift to higher frequencies, confirming that there are intermolecular interactions in the solid state. The observed frequencies are consistent with the acids being lactones of γ-hydroxy-β-keto-carboxylic acids in the enolic form. The wavenumber-range from 1740-1750 cm\(^{-1}\) was assigned to the five-ring lactone-carbonyl-group, those around 1630 cm\(^{-1}\) correspond to the C=C-stretching modes. \(\alpha\)-Acetyltetronic acid is less effected by dissolution. This is also shown by varying the solvent. The keto-enol-equilibrium of tetronic acid and \(\gamma\)-methyl tetronic acid is present with the enol-form predominating in chloroform. The use of 1,2-dichloroethane as solvent alters a equilibrium dominated by the keto-form. This insight is confirmed by the almost complete disappearance of the endo-cyclic C=C-stretching mode frequency in the discussed cases. An \(\alpha\)-alkyl substitution seems to stabilize the enolic form, why in the case of \(\alpha\)-ethyltetronic acid there is no evidence for an emerging keto-form in 1,2-dichloroethane. The variation of the solvent does not cause any significant frequency-shifts in the absorption of \(\alpha\)-acetyltetronic acid.

Figure 5.9: Absorption Spectra of some Tetronic Acids, Duncanson 1953

Conclusively, it could be stated, that the possibility of \(\alpha\)-acetyltetronic acid
to form strong intramolecular hydrogen-bonding leads to a certain insensitivity to environmental changes - being the state of matter or the solvent applied, respectively. But Duncanson only compared five model substances. To verify and generalize these statements more α-acylated tetronic acids have to be examined in this regard.

Mecke and Funck did an investigation concerning keto-enol-tautomerism on acetylacetone [40]. Their merit was an almost complete vibrational analysis of acetylacetone by systematical variation of temperature and solvent influences. They also examined the spectra of single-valence metal chelates (Li, Na, K, Tl(I), Ag(I)). In this complexes the enol-form is fixed. The hydrogen-bridge is then substituted by the metallic equivalent. This technique gave the spectroscopists important hints during the assignment of the spectral features. The first IR-measurements of metallic acetylacetonates were made by Lecomte in 1939 [41]. It took more than ten years to assign and to understand the spectra. But finally, Lecomte et al. succeeded with the assignment [42, 43].

Determining the strength of an intermolecular hydrogen-bonded system via IR spectroscopy has been problematic because of several factors: The OH-stretching vibration is broad and weak, hence the assignment of its centre is extremely difficult. The C=O-stretching can be perturbed by the C=C-stretching vibration, and the hydroxyl in-plane deformation vibration often coincides with the C-O-stretching and alkyl bending deformation vibrations revealing no informations. Furthermore, the OH-out-of-plane deformation, \( \pi(\text{OH}) \), can be found at similar wavenumbers like the methyl group rocking or in-plane C-H-deformation [44]. For that reason, \( \nu(\text{OH}) \) and \( \pi(\text{OH}) \) are not suitable for the purpose of determining the strength of intramolecular hydrogen-bonding.

Ogoshi et al. provided a method, which overcomes these problems [45]. By shaking a solution of the sample with \( \text{D}_2\text{O} \) or \( \text{CH}_3\text{OD} \) the enolic proton is deuterated. The \( \pi(\text{OD}) \) vibration stands almost alone in the range of 580-750 cm\(^{-1} \) as a new band. The OD-out-of-plane deformation can be regarded as a torsional vibrational mode around the C-O bond of the enolic ring and thus, should be a measure of the double-bond character of the C-O bond (cf. [46]). But anyway, these measurements have not been made on 3-acyltetronic acids.

In 1974, a first insight to the energetics of intramolecular hydrogen-bonding in connection with \( \pi \)-electrons was given by Kopteva and Shigorin [47]. The energy
of a hydrogen-bond is given by the equation:

\[ E = E_{\text{dipol}} + E_{\text{donor/acceptor}} + E_\pi \]

The formation of hydrogen-bonds in systems with \( \pi \)-electrons can lead to a quasi-aromatic charge delocalization (formation of a planar six-membered ring): six \( \pi \)-electrons are provided by the C=C-, C=O-bonds and a lone-pair of the hydroxyl-oxygen. The band-centres of the hydroxyl-stretching vibration were assigned and the band intensities were integrated. Afterwards, the shift of the band-centres was correlated with the square-root of the integrals of the corresponding band-intensities to give an antiproportional relation. The frequency shifts were determined against a reference value of \( \nu_0 = 3620 \text{ cm}^{-1} \). The formation of a hydrogen-bond is characterized by changes in the vibration frequencies of the corresponding groups and by a change of the integrated intensity, as well as by the appearance of the frequency corresponding to the hydrogen-bond \(-\text{H} \cdots \text{O}\).

Furthermore, it has been observed that the integrated intensity of the involved hydroxyl group increases sharply upon hydrogen-bond formation - up to 10 times corresponding to the free groups. These findings can be related to changes in the charge distribution of the whole molecule and in the dipole moments of the groups participating in the corresponding vibrational mode due to the enhanced delocalization.

An investigation on dicarbonyl compounds’ enol forms and the description of the spectral features - also on acetyl tetronic acid - was carried out by Grens et al. in 1975 [48]. They describe a general absorption spectrum of intramolecularly associated cis-enols as follows: One feature is one multiple or several bands in the region of 1500-1800 cm\(^{-1}\) belonging to double-bond (C=O and C=C) stretching modes, depending on the chemical structure. The \( \nu(\text{OH}) \) band reaches as a very broad and diffuse band in the spectral region of 2200-3400 cm\(^{-1}\) with a maximum at 2600-2900 cm\(^{-1}\). The structure of this band does neither depend on solvent properties, nor on the chemical structure of the compound, according to the findings of Duncanson. The assignment of the \( \nu(\text{OH}) \) band was confirmed by deuteration experiments. For 3-acetyltetronic acid the absorption maximum of \( \nu(\text{OH}) \) can be found at 2950 cm\(^{-1}\) and \( \nu(\text{OD}) \) is situated at 2180 cm\(^{-1}\). In comparison, cyclic \( \beta \)-dicarbonyl compounds like 5,5-dimethylcyclohexane-1,3-dione are not able to form intramolecular hydrogen-bonded cis-enols. They occur as
trans-enols for sterical reasons.

Avakyan and coworkers did in 1995 a spectroscopic and quantum-chemical investigation of the tautomeric properties of 3-acetyltetronic acid [49]. Utilizing the calculated IR data (AM1 semiempirical level) of 2-acetyl-1,3-cyclopentadione as a model compound they were able to assign many of the vibrations of the different tautomers of 3-acetyltetronic acid. The assignment was also supported by Raman-data. The most important results were the assignment of many spectral features and the characterization of the tautomeric mixture in the gas-phase and in solution of chloroform. The two tautomeric forms with \textit{exo}-cyclic C=C-double-bonds dominate the mixture. However, the \textit{exo}-cyclic tautomer with the lactone-group taking part in the intramolecular hydrogen-bond dominates a little over the corresponding keto-involved tautomer in the gas-phase. This also applies for solutions of 3-acetyltetronic acid in chloroform or tetrachloromethane. But also a minor amount of the \textit{endo}-cyclic keto-involved tautomer could be observed. Their results contradict the order of stability found by means of NMR-measurements. This could be due to the wrong assignment of the NMR-data. The investigators chose 5,5-dimethylacetylcyclohexane-1,3-dione as an analogue, which should behave differently from a five-membered \(\beta,\beta'-\)triketone. Conclusively, they stated, that five-membered \(\beta,\beta'-\)triketones exist predominately in \textit{exo}-tautomers, whereas the six-membered relatives occur preferably as \textit{endo}-cyclic double-bonded tautomers. They also tried to get insight to the behaviour of 3-acetyltetronic acid in the solid state, but unfortunately, they did not succeed, because they got contradictory IR- and Raman-data. The prevailance of the \textit{exo}-enols could also be stated for the more complicated 3-[3-(4-methoxycarbonylphenyl)acryloyl]tetrahydrofuran-2,4-dione [50], also by the supplemental use of IR-spectroscopy and quantum-chemical calculations.

### 5.4 Raman Spectroscopy

In general, Raman spectroscopy gives complementary data to IR-spectra. A molecular vibration is called IR-active and has a absorption unequal to zero when a change of the dipolemoment happens during the vibration. Raman activity is characterized by a change in the polarizability of a molecule. Hence, also symmetric vibrations can be detected [51]. In 1943, Edsall and Sagall did a
5.5. UV/VIS SPECTROSCOPY

Rudimentary investigation on ascorbic acid, tetronic acid and related compounds [52]. They focussed on the change of some spectral features upon ionisation by comparing the spectra of aqueous solutions of the acid and its sodium salt. Whereas ascorbic acid and its derivatives shows a significant change of the Raman spectra upon ionization, the tetronic acid’s spectra remained comparable. A line of moderate intensity at 1727 cm$^{-1}$ vanishes on ionization. The line at 1680 cm$^{-1}$ becomes more intense in the ion. A line at 1580 cm$^{-1}$ is not affected by ionization. These results were not interpreted by the authors. Their aim was merely to record and to compare spectra. Later, Raman measurements have been made by Avakyan et al. [49] on 3-acetyltetronic acid. They used Raman spectra in combination with IR data and quantum mechanical calculations. Thereby, they succeeded in assigning many of the Raman lines corresponding to IR lines of 3-acetyltetronic acid in solution and in the solid state. The results of this investigation have been presented in section 5.3.

5.5 UV/vis Spectroscopy

In 1935, Herbert and Hirst [53] made experiments on the UV/vis-absorption of 3-ethyl- and 3-acetyltetronic acids, as well as on the metabolic acids of *Penicillium Charlesi*. 3-Ethyltetronic acid shows only one single intense band in an aqueous solution at $\lambda=258$ nm, which changes by adding an acid or alkaline, whereas 3-acetyltetronic acid, as well as carolic-, carlic-, carolinic- and carlosic acid (cf. section 2.1) show two intense absorptions at $\lambda=200$ nm and $\lambda=200$ nm. On the one hand, these bands are modified in comparison to 3-ethyltetronic acid, on the other hand, they do not change appreciably by adding an acid or alkaline. These positions indicate, that all these compounds are of the same manner. Furthermore, the absorption spectra of carolic and carlic acid display only one single absorption band in a non-aqueous medium (dry alcohol) at $\lambda=270$-$272$ nm, which indicates a difference in structure between the hydrated and the non-hydrated forms.

The series of observations was extended by investigations of various structurally related acids, such as 5-methyltetronic acid, whose absorption is identical with those of the other types, also 5-carboxymethyltetronic acid has a similar absorption spectrum.
Also Lacey has established [54], that 3-acetyltetronic acids exhibit two absorption bands at $\lambda=230-236$ nm and at $\lambda=260-268$ nm. He supplemented, that this absorption behaviour is similar to enolized $\beta,\beta'$-triketones.

### 5.6 Crystallography

A bunch of structural data of $\beta$-dicarbonyl compounds has been acquired by means of X-ray diffraction, though it is not the best technique for determining the position of hydrogen atoms due to their low electron density [14]. To locate hydrogen atoms one has to apply neutron scattering methods, which are apparatively far more complicated. A natural measure of the strength of a hydrogen-bond in $\beta$-dicarbonyl compounds is the contact distance $d_{O-O}$ between the two oxygen atoms. This value can certainly be obtained by means of X-ray crystallography. Amongst the first molecules examined by X-ray diffraction were the $m$-chloro and $m$-bromo derivatives of dibenzoylmethane [55, 56]. They proved to have short hydrogen-bond lengths and $d_{O-O}$ of approximately 2.47 Å. The hydrogen atom was supposed to be situated centrally between the two oxygen atoms, though it could not be located. In 1994, Barkley et al. worked on the related tetramic acid [57]. They published the X-ray structures of N-acetyl-3-butanoyltetramic acid with the result, that the solid compound exists in a tautomeric form with an endocyclic double-bond. The acyl-oxygen is pointing away from the lactame-group. Gilli and coworkers used X-ray and neutron diffraction methods extensively to get an insight in the hydrogen-bonding properties of $\beta$-dicarbonyl systems (cf. therefore section 3.2). However, crystallographic methods have not been applied systematically to 3-acyltetronic acids in order to disclose the molecular structure of this compounds, yet. Similarities to the closely related tetramic acids should be expected.

### 5.7 Molecular modeling

The first calculations concerning the relative stability of the four enol forms of 3-acetyltetronic acid (Fig. 5.10) were made by Avakyan et al. [49].

They used ab initio calculation with a 3-21G standard valence basis set and the semiempirical AM1 method to estimate the relative thermodynamic stabil-
Figure 5.10: Four Enol Forms of 3-Acyltetronic Acid

Ities and for geometry optimisation. They showed, that both exo-enols (b,d) are comparable in their thermodynamic stability (0.6 kcal/mol) and are energetically preferred relatively to endo-enols, which confirms the IR spectroscopic observation. The calculated energy difference between b and d was too small to decide with confidence which of the compounds is more stable. They expect, that structure d is less preferred, because lactonic carbonyl groups are supposed to form weaker H-bonds in comparison to acyclic ketones. The endo-enols are more energetically distinguished than the exo-enols, the conformer a is more stable.

Further examinations were made by Avakyan et al. [58] with the aim to evaluate the relative thermodynamic stability of all the possible tautomeric forms of 3-formyl-tetronic acid (Fig. 5.11). This compound suits as a model for investigating the tautomerism of 3-acyltetronic acids and to study the theoretical vibrational spectra of enol forms a,d.

They used ab initio calculations, which have been carried out with full optimization of the geometric parameters according to the Møller-Plesset second-order perturbation theory with the use of a 6-31G(d) double zeta basis set (MP2/6-31G(d)//MP2/6-31G(d)). The correlation corrections to the total energy of molecules for optimized geometric configurations have been calculated according to the Møller-Plesset fourth-order perturbation theory in the 6-311G(d,p) basis (MP4/6-311G(d,p)//MP2/6-31G(d)). The relative thermodynamic stabil-
ity and the harmonic vibrational frequency for fully optimized geometries of all structures have been calculated by the density functional theory (DFT) method.

The calculation of the harmonic vibrational frequencies for the transition states of the proton transfer reactions has revealed the presence of one imaginary frequency for each of them. Calculations of the relative content in the gas phase according to the Møller-Plesset fourth-order perturbation theory led to the main proportion of 2d and to a very small amount of 2c, the enolic form 2a is more preferred than 2b. The form c is about 3.5 kcal/mole more unstable than the other ones, which differentiate only around 0.5 kcal/mole, depending on the used basis set. The strongest intramolecular hydrogen bonding was calculated for the form a, the weakest for the form b.

Calculations on the basis of density functional theory for 3-acetyltetronic acids (Fig. 5.10) provided the confirmation of the results received six years earlier by \textit{ab initio} calculations [49]. But this time, they could proceed on the assumption, that for the \textit{exo}-enols, 1d is more stable than 1b (0.46 kcal/mole) by using a more reliable method. Comparison of the calculated intramolecular hydrogen-bonding energies shows, that (MP4/6-311G(d,p)//MP2/6-31G(d)) calculations yield results, that are the closest to the experimental data.

The calculated vibrational frequencies \( \nu(\text{OH}) \) of the forms 2a, 2b and 2d correlate with the obtained energy values of their intramolecular hydrogen-bondings.
For 2c, however, such a dependence is not observed. One of the main results of the \textit{ab initio} calculations of the vibrational spectra of 2a, 2b, and 2d is the fact, that the stretching vibration frequencies of lactonic C=O groups are higher than the $\nu$(C=O) of ketonic groups irrespective of their participation in the intramolecular hydrogen-bond formation. The vibration frequencies obtained by the DFT calculation greatly differ from those calculated by the \textit{ab initio} method. For a proper correlation of the \textit{ab initio} vibrational frequencies with the experimental data scale-factors are necessary. DFT-calculations are able to predict IR-spectra of this compounds with a satisfactory accuracy. Two years later, Skylaris \textit{et al.} also published their density functional and \textit{ab initio} studies on the tautomeric forms of 3-acetyltetronic acid [59]. They used the density functional theory method with the B3LYP hybrid function for geometry optimization and the \textit{ab initio} second order Møller-Plesset perturbation theory (MP2), as well as the B3LYP functional for single point energy calculations with a pTZV basis set. All possible structures and transition states were calculated, a simplified scheme is shown in Fig. 5.12.

Several structures of \textit{e} were found, which differentiate in different dihedral angles and in various angles of the acetyl methyl group referring to the ring system. Every structure of \textit{e} shows an equilibrium to one of the most stable forms \textit{a}, \textit{b}, \textit{c} or \textit{d} via one transition state. In general, their results agree with these of Avakyan \textit{et al.} as mentioned above. By the DFT method they calculated, that form \textit{d} is the most stable one and the form \textit{c} the most unstable one among the hydrogen-bonded tautomers ($\Delta E = 21.1$ kcal/mole). The energy value of the transition state between them (\textit{cd TS}) is very closed to this of \textit{c} ($\Delta E = 23.0$ kcal/mole relative to \textit{d}). The rotation barrier of these ”internal” tautomers to the other ”internal” tautomers \textit{a} and \textit{b} amounts to 170.0 kcal/mole. They show values of $\Delta E = 9.2$ kcal/mole for \textit{a} and $\Delta E = 2.0$ kcal/mole for \textit{b}. The value of the transition state between them adds up to $\Delta E = 19.7$ kcal/mole. All values are given relatively to \textit{d}. Finally, they could show, that the rotation barrier between the two ”internal” tautomers is much higher than that between \textit{a} and \textit{b}, as well as \textit{c} and \textit{d}, respectively. This is in agreement with the described NMR observations. By using the MP2 method, the energies show the same tendency with very similar values. The calculation of the Gibbs free energies at room temperature causes a decrease of the values relative to \textit{d}. The form \textit{a} is even a little more stable than \textit{d} ($\Delta E = -0.85$ kcal/mole). Also the calculated $^1$H-NMR and $^{13}$C-NMR shifts are
Figure 5.12: Simplified Scheme after Skylaris
in very good agreement with the experimental results.

Frontier orbital calculations show, that the HOMO of d has mainly $\pi$-bonding character and its magnitude is large above and below C-3, what indicates, that this area has an affinity for reactions with electrophiles. In contrast, the HOMO of e has mainly $\sigma$-bonding character and is not available to reactants. Gromak et al. have calculated the energies of the intramolecular hydrogen bonds of the endo- and exo-enolic tautomers in 2-formylcyclopentane-1,3-dione for the first time [60]. Due to their symmetry, they appeared to be equal (3.69 and 4.91 kcal/mole, respectively) in contrast to 3-acetyl tetronic acid, whereas the calculated zero point vibrational energies show the same tendency. This is not astonishing, since this compound represents the basic frame of 3-acetyl tetronic acid.

Gromak et al. also made ab initio and DFT calculations on 3-[(4-methoxy-carbonylphenyl)acryloyl]tetrahydrofuran-2,4-dione [50] (Fig. 5.13) with the same methods as used for 3-acetyl tetronic acids. The ab initio calculations predict a relatively low content of the endo-enolic forms 3a and 3c in an equilibrium mixture. Their results allow to assume the absolute domination of the forms 3b and 3d. They show a very small difference in energy, much smaller than in 3-acetyl tetronic acid (0.35-0.73 kcal/mole, depending on the used method). When the AM1 method is used, the enolic form 3b is even more stable than 3d, but this method has a low accuracy. More accurate nonempirical methods give the enolic form 3d as the most stable form. This is analogous to 3-acetyl tetronic acid, just as the preferred exo-enolic tautomers.
Figure 5.13: 3-[3-(4-methoxycarbonylphenyl)acryloyl]tetrahydrofuran-2,4-dione
Chapter 6

Synthetic Strategies

6.1 Synthesis of Tetronic Acids - a Historical Survey

Before beginning with the real programme - the synthesis of 3-acyl(thio)tetronic acids - a brief historical outline of the tetronic acid’s chemistry will be given based on a review article of Haynes and Plimmer in 1960 [61]. The roots of the chemistry of tetronic acids in general were laid by Demarçay in 1880 [62]. One can distinguish between three complete different approaches of tetronic acid’s syntheses. These are the cyclisation of γ-halogeno or γ-acetoxy-acetoacetic ester derivatives. It was Wolff, who prepared for the first time tetronic acid [63, 64] by following this route. Extension to the early protocols were given by Benary [65] and Anschütz [66, 67, 68].

A further way to tetronic acids is the hydration of α, β-acetylenic γ-hydroxy acids. The general scheme is the addition of secondary amines or alcohols to α, β-acetylenic γ-hydroxy acids followed by hydrolysis of the product. The lactonisation happens spontaneously. This route was employed by Jones and coworkers [69, 70].

The third way is the Dieckmann-Cyclization approach - the condensation of α-acyloxy-esters. This way was first reported with regard to 4-hydroxycoumarin synthesis [71, 72], but later it was applied to five-membered lactones (i.e. tetronic acids) by Haynes and Stanners [73, 74, 75]. The furtherly discussed method of Lacey [54] furnishes 5-substituted α-acetyltetronic acids by applying this ringclosure reaction to β-ketoester of 2-hydroxyesters.
6.2 Synthesis of 3-Acyltetronic Acids

Because of the biological interest of some 3-acylated tetronic acid derivatives many efforts have been made to set up high-yielding, facile and stereocontrollable synthetic procedures. They can be classified coarsely into two general types: i) Dieckmann-type cyclizations of acetoacetates and ii) acylation of 3-unsubstituted tetronic acids. In the next subsections the synthetic methods belonging thematically together are presented in an almost historical order.

6.2.1 First attempts towards the synthesis of 3-Acyltetronic Acids

Benary [76] recognised during his investigations of the action of β-keto compounds on chloroacetylchloride, that ethyl β-aminocrotonate reacts similarly to ethyl acetoacetate in a C-acylation. By reacting ethyl β-aminocrotonate with chloroacetylchloride in anhydrous ether in the presence of pyridine he isolated the C-acylated species ethyl α-chloroacetyl-β-aminocrotonate (Fig. 6.1a) in 75 % yield. This compound cyclized almost quantitatively upon heating to 140-160 °C for 15 min and loss of chloroethane to give compound b - the amide of α-acetyltetronic acid. The amide was then deaminated by alkaline hydrolysis to the desired 3-acetyltetronic acid (Fig. 6.1c). Benary did not state a yield for the deamination step.

$$\begin{align*}
\text{NH}_2\text{O} - \text{O} \quad + \quad \text{Cl} - \text{O} - \text{Cl} \\
\text{in ether} \\
\text{NH}_2\text{O} - \text{O} - \text{Cl} \\
\text{15 min at} \\
\text{140-160 °C}
\end{align*}$$

$$\begin{align*}
\text{NH}_2\text{O} - \text{O} - \text{Cl} \\
\text{1.) NaOH} \\
\text{2.) acetic acid} \\
\text{-NH}_3
\end{align*}$$

Figure 6.1: Benary’s Approach to 3-Acetyltetronic Acid

Later publications gave extensions and optimizations to Benary’s method.
Baker, Grice and Jansen picked up Benary’s ideas and published in 1943 a simplified method [77]. They prepared the anilide of 3-acetyltetronic acid (Fig. 6.2c) and hydrolysed it instead of the amide.

![Chemical diagram]

Figure 6.2: An Optimized Version of Benary’s Method

This method gave 43 % yield of the anilide (referring to methyl acetoacetate) and the deamination produced the acyltetronic acid with 80 % yield. An overall yield of 34.4 % makes a further optimization of this synthetic approach necessary.

Lecocq applied Benary’s method in 1946 [78] to synthesize γ-monosubstituted α-acetyltetronic acids. For that purpose α-bromopropionylbromide or α-bromo-phenylacetylchloride, respectively, were used instead of chloroacetylchloride. In this way the first 5-substituted acyltetronic acids were made. They are of special interest because of their relation to the biologically active carolic and carolinic acid, which were isolated from mould cultures (Penicillium Charlesii) in 1934 by Clutterbuck et al. [79].

In the course of a systematic study on the acylation of β-dicarbonyl compounds with acid chlorides and their cyclization Gelin and Galliaud observed, that the cyclization of their starting material did not lead directly to the desired acyl tetronic acids, but to another five-membered ring [80]. This could be converted to a 3-acyltetronic acid by treatment with aqueous sodium hydroxide following the mechanism shown in Fig. 6.3 with overall yields of 54-57 % for the shown substituents.
6.2.2 Cyclization of Acetoacetates of 2-Hydroxyesters

A higher yielding method was invented by Lacey in 1954 [54]. In his treatise on derivatives of acetoacetic acid he proposed a preparation procedure including a Dieckmann-Cyclization of acetoacetates of 2-hydroxyesters which proved to be the most widely used synthetic approach to substituted 3-acyltetronic acids nowadays.

To obtain the precursors the corresponding 2-hydroxyester (e.g. ethyl glycolate, (S)-(−)-ethyl lactate, ethyl 2-hydroxy-iso-butyrate or ethyl DL-mandelate) was heated with diketene and triethylamine as a catalyst. Then the acetoacetate of the β-hydroxyester was cyclized by heating with a base. Different bases were tried out by Lacey, amongst them sodium in toluene, alkali ethoxides in toluene and alkali tert-butoxides. To cyclize esters of the type $R_2 = R_3 \neq H$, sodium ethoxide in toluene turned out to be the best base to afford the Dieckmann-Cyclization. The ringclosure to γ-monosubstituted tetronic acids was carried out with sodium in toluene to give the highest yields. Nevertheless, Lacey did not succeed in synthesizing 5-unsubstituted acyltetronic acids. Actually, he did not discuss this problem in his publication at all.

The main disadvantage of the use of diketene as a reactant is, that only 3-
acetyl-tetronic acids are procurable. Changes in the acyl moiety call for other precursors than diketene.

Later on, in a couple of papers Lacey’s procedure was discussed and partially optimized or extended. In that way did Bloomer and Kappler, who applied potassium tert-butoxide in tert-butanol successfully to the cyclization of the acetoacetate of ethyl (RS)-lactate to gain a yield of 95 % [3]. To compare: Lacey obtained 50 % with sodium in toluene as a base. Although he tried potassium tert-butoxide as cyclization agent he only got a poor 46 % yield. It seems that Bloomer and coworkers were more handy than Lacey. This shows, that reaction yields stated in literature do not only depend on the described method and the reaction conditions, but also on the chemist’s skills doing the reaction.

The problem of the use of diketene and its restricted product pallet was overcome by Ley and coworkers in 1983 [81, 82]. They invented a different route to the precursors of the β-ketoesters of 2-hydroxyesters. Starting with the regioselective alkylation of the dianion of tert-butylacetothioacetate in dimethoxyethane (DME), a transesterification of the latter product with a 2-hydroxyester furnished the desired β-ketoesters. These could be cyclized in the common way. Tetra-n-butylammonium fluoride (TBAF) in tetrahydrofuran (THF) was used preferably as a cyclization reagent to give good to excellent yields. Changes in the acyl moiety can now be readily achieved by variation of the alkylation reagent (R₁X in Fig. 6.5).

Another great advantage are the mild cyclization conditions. To effect the
ring closure the ester is simply stirred with TBAF in THF under argon atmosphere at room temperature for several hours. In this way the natural product (S)-carlosic acid could be prepared in 60 % overall yield. The versatile use of the fluoride ion as a base in organic synthesis has been reviewed by Clark in 1980 [83].

In the late 1980’s, the problem of the cyclization of γ-unsubstituted α-acyl-tetronic acids was still not solved. Ager and Mole encountered this difficulties on their way to antibiotic compounds. So, they did a systematical investigation on different cyclization reagents [84]. The outcome was an adjustment of Lacey’s reaction conditions. It proved, that refluxing the starting ester with sodium tert-butoxide in tert-butanol was the best cyclization method in the case of an ethyl ester. They also tried out iso-propyl esters and established potassium tert-butylate in tert-butanol and TBAF/THF to be the most adequate base systems.

Ager and Mole also attempted an interpretation of the influence of different bases and solvents used for the cyclization reaction. The transition state of the cyclization seems to be very crowded (cf. Fig. 6.6). The larger the substituents R₂ and R₃ are, the more the conformation leading to the ring closure is favoured, viz. the preferred conformation prior to cyclization seems to be an open chained. In the unsubstituted cases these interactions are at a minimum. A metal counterion providing an enolate with a significant ionic character is required for the

Figure 6.5: New Way to β-Ketoesters of 2-Hydroxyesters and their Cyclization
transformation, which is also supported by the use of polar solvents.

Kaneko and coworkers proposed a new way to \( \beta \)-ketoesters of 2-hydroxyesters, namely via the acylation of \( \alpha \)-hydroxyesters by acylated Meldrum’s acids [85]. Therefore, the appropriate acyl-Meldrum’s acid was transferred into the corresponding dioxinone. This has to be boiled in an aprotic solvent (toluene) containing the 2-hydroxyester, yielding the \( \beta \)-ketoester of the 2-hydroxyester, which was then cyclized by n-Bu\(_4\)NF in THF at room temperature.

In their series ‘Heterocyclic Analogs of Prostaglandines’ Pashkovskii et al. used the protocol of Sato and coworkers to prepare 3-acyltetrionic acids with long side-chains in the acyl moiety [8]. Beginning with the acylation of Meldrum’s acid (isopropylidene malonate) by the action of the appropriate acid in the presence of a catalytic amount of 4-N,N-dimethylaminopyridine (DMAP) and 1.2 equivalents of dicyclohexylcarbodiimide (DCC), they treated the acidic tricarbonyl compound (Fig. 6.7 b) with acetone in boiling toluene to obtain the neutral 1,3-dioxin-4-one \( c \). This can be thermolysed to give a \( \alpha \)-ketoketene intermediate \( d \). The 1,3-dioxin-4-one was purified by chromatography on aluminium oxide and afterwards heated with an equimolar amount of 2-hydroxyester (here: ethyl lactate). So, \( \beta \)-ketoesters of 2-hydroxyesters \( e \) were prepared. Finally, the Dieckmann-Cyclization was afforded with tetra-n-butylammonium fluoride to build the tricarbonyl functionality of a 3-acyltetronic acid. In this way it was possible to prepare \( \gamma \)-methyl-\( \alpha \)-nonanoyl tetronic acid with an overall yield of 53%.

The Dieckmann-Cyclization of a slightly different type of ester was applied by Ley and coworkers in 1998 as the last synthetic step in the total synthesis of tetronasin [86], an acyltetronic acid ionophore with antibiotic and antiparasitic effects. The preparation was a challenging project because of tetronasin’s twelve stereogenic centres, three different heterocycles, two stereodefined alkenes and a triequatorially substituted cyclohexane ring (cf. Fig. 6.8).
CHAPTER 6. SYNTHETIC STRATEGIES

Figure 6.7: β-Ketoester of 2-Hydroxyesters via acylated Meldrum’s Acids

Figure 6.8: Tetronasin
6.2. SYNTHESIS OF 3-ACYLTETRONIC ACIDS

6.2.3 Acylation of 3-unsubstituted Tetronic Acids

Following the historical order, the next approach to 3-acylated tetronic acids was to acylate α-unsubstituted tetronic acids in a Friedel-Crafts-Acylation. The first successful attempts were published by Haynes and Jamieson in 1958 [87]. By reacting γ-phenyltetronic acid with acetyl chloride in the presence of several Lewis-acids they obtained - although in poor yields - the acylated tetronic acid. The best Lewis acid to use was tin(IV) chloride in 1.3 equivalent amount. Also γ,γ-disubstituted tetronic acids have been examined as starting materials. Here the yields rose up to 50%. However, their method was restricted to acetylations. Experiments with higher acyl chlorides were not successful.

\[ \text{O} \quad \text{O} \quad \text{R}_3 \quad \text{R}_2 \quad + \quad \text{Cl} \quad \text{O} \quad \text{O} \quad \text{R}_1 \quad \text{R}_3 \quad \text{R}_2 \quad \text{HO} \quad \text{R}_1 \]

Figure 6.9: Friedel-Crafts-Acylation of Tetronic Acids

In connection with Friedel-Crafts-Acylation investigations Haynes and Jamieson examined the Fries-Rearrangement, which usually can be observed at phenyl esters. At first, an enol ester of a tetronic acid has to be prepared by reaction of a tetronic acid with acetic anhydride. This can then rearrange in the presence of a Lewis-acid catalyst added in 1.3 equivalent excess to the corresponding α-acyltetronic acid. In this manner they succeeded in preparing several α-acetyl and α-benzoyltetronic acids in acceptable yields.

\[ \text{O} \quad \text{O} \quad \text{R}_3 \quad \text{R}_2 \quad \text{acetic anhydride} \quad \text{[H}_2\text{SO}_4] \quad \text{r. t.} \quad \text{O} \quad \text{O} \quad \text{R}_3 \quad \text{R}_2 \quad \text{HO} \quad \text{R}_1 \]

Figure 6.10: Fries-Rearrangement within Tetronic Acids

In 1974, Lehmann and Wamhoff did a systematic investigation on Fries-Rearrangements of O-acetyltetronic acids [88]. They also tested in addition to
Haynes et al. mono- and unsubstituted O-acetyltetronic acids. Heating of these compounds in water or ethanol resulted preferably in a loss of the acetyl rest to give tetronic acids and not the desired acetylated species. Toluene or benzene as solvent with a catalytic amount of polyphosphoric acid proved to be the most appropriate system to run the reaction in.

Andresen et al. synthesized a row of 3-acyltetronic acids utilizing a slight modification of Haynes' method [89]. They also achieved the synthesis of (RS)-Carolic and (S)-Carolic acid.

Driven by synthetic problems concerning natural products Clemo and Patten-den invented an acylation method for the preparation of complex 3-acyltetronic acid derivatives [90, 91]. Applying lithiumdiisopropylamide (LDA) in THF to an O-methyl tetronic acid a vinylic carbanion was created. This can react with various electrophiles. In Fig. 6.11 the carbanion \( a \) was treated with methylacrylate to give the acylated tetronic acid derivative \( b \).

![Figure 6.11: Creation of a Vinylic Carbanion and its Trapping with Methylacrylate](image)

The use of vinylic carbanions of tetronic acid derivatives was also demonstrated with the syntheses of \( \text{iso} \)-gregatin B and \( \text{iso} \)-aspertetronin A (see Fig. 6.12) [91, 92]. These compounds are the enol ether isomers of gregatin B and aspertetronin A found in \( \text{Aspergillus sp.} \) and \( \text{Cephalosporium gregatum} \), respectively.

Yoshii and coworkers published a modification of the latter acylation method for the preparation of several 3-acyltetronic acid derivatives [93]. In the main their procedure includes the lithiation of the appropriate 3-bromotetronic acid with n-butyllithium followed by an acylation with an acid chloride. Instead of the acylchloride the corresponding aldehyde could be used. The resulting carbinol is then oxidized with activated \( \text{MnO}_2 \) (cf. Fig. 6.13).

Yoshii himself developed this method further to give another extension of the
6.2. SYNTHESIS OF 3-ACYLTETRONIC ACIDS

\[ \begin{align*}
iso\text{-}gregatin\ B\: & \quad iso\text{-}aspertetronin\ A \\
\end{align*} \]

Figure 6.12: Isomers of Natural Products synthesized \textit{via} a Vinylic Carbanion

\[ \begin{align*}
\text{H}_3\text{CO} & \quad \text{O} \\
\text{H}_3\text{CO} & \quad \text{O} \\
\text{H}_3\text{CO} & \quad \text{O} \\
\text{H}_3\text{CO} & \quad \text{O} \\
\end{align*} \]

Figure 6.13: Acylation of lithiated Tetronic Acids after Yoshii \textit{et al.}
acylation procedure [94]. By choosing other reagents he optimized the method for systems bearing base sensitive functional groups. After an O-acylation of the \(\alpha\)-unsubstituted tetronic acid, 4-N,N-dimethylaminopyridine (DMAP) was used to effect an O→C(3)-rearrangement (cf. Fig. 6.14). O-acylation was caused by the action of an acid anhydride or the corresponding acid in combination with dicyclohexylcarbodiimide (DCC) in both cases with triethylamine as a catalyst. The O-acylated intermediate was not isolated. This one-pot procedure’s main advantages are the mildness of the reaction conditions and furthermore good to excellent overall yields (55-94 %).

![Figure 6.14: A Mild One-pot Acylation Procedure proposed by Yoshii et al.](image)

6.2.4 Cycloaddition Approach to 3-Acyltetronic Acids

Jones et al. set up a synthetic procedure for 3-acyltetronic acids, in which the polar functionality of the tricarbonyl moiety is masked until a late stage in the synthetic sequence [95]. 1,3-dipolar cycloaddition of nitrile oxides to enamines formed from protected \(\gamma\)-hydroxy-\(\beta\)-keto esters leads to isoxazolecarboxylic esters, that can be converted in 3-acyltetronic acids.

Starting from ethyl acetoacetate, which is transformed to the tert-butyl-\(\beta\)-keto ester, the pyrrolidine enamine is prepared. A 1,3-dipolar cycloaddition of acetonitrile oxide - prepared \textit{in situ} by dehydratation of nitroethane by phosphoryl chloride - to the enamine (Fig. 6.15 \(d\)) furnishes the 5-ethoxymethylisoxazole \(e\) with 63 % yield. Alkaline hydrolysis of the ester function gives the corresponding acid \(f\), which is then activated by ethyl chloroformiate to a mixed anhydride \(g\). The action of hydrogen bromide in acetic acid on the anhydride causes a N-O-cleavage yielding an enamine salt \(h\) and not the expected furoisoxazolone \(i\) via a cyclization of the anhydride. The enamine salt could be readily converted to the desired product: 3-acetyltetronic acid.
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Figure 6.15: Synthesis of 3-Acetyltetronic Acid via 1,3-dipolar Cycloaddition
6.2.5 Cyclization of Active Esters of \(\alpha\)-Hydroxyacids

Anschütz \textit{et al.} described in 1903 the reaction of \(\alpha\)-acetylglycolic acid ethyl ester with active methylene compounds like sodium dimethyl malonate \cite{68}. After refluxing the reactants in benzene for 20 hours an acidic work-up followed to give the 3-methoxycarbonyl tetronic acid.

Mitsos \textit{et al.} picked up this idea in 2000 in search of a new stereospecific synthesis of chiral tetronic acids \cite{96}. Therefore, they used the optically pure enantiomers of malic acid as chiral precursors. The acid was transformed to the O-acetylated cyclic anhydride by heating with acetylchloride. This could easily be opened with an anion of a \(\beta\)-ketoester. The crude intermediate Fig 6.16 \(b\) was subsequently deacetylated and cyclized under basic conditions to provide the desired 3-acyl-5-carboxymethyltetronic acids \(c\) in overall yields of 51-79 \%.

\begin{equation}
\begin{array}{c}
\text{HO} & \text{OH} & \text{O} & \text{O} & \text{Cl} & \text{O} & \text{O}\text{Ac} \\
\text{OH} & \text{OH} & \text{O} & \text{OR} & \text{R}^1 & \text{O} & \text{O} \\
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{OH} & \text{OAc} & \text{O} & \text{O} & \text{OH} & \text{R}^1 \\
\text{OH} & \text{O} & \text{O} & \text{O} & \text{OAc} & \text{OR} & \text{R}^2 \\
\end{array}\end{equation}

\begin{equation}
\begin{array}{c}
\text{HO} & \text{OH} & \text{O} & \text{O}\text{Ac} & \text{O} & \text{OR} & \text{R}^1 \\
\text{1.) 2 N NaOH in MeOH} & \text{1.) 2 N NaOH in MeOH} \\
\text{2.) 10 \% HCl} & \text{2.) 10 \% HCl} \\
\end{array}\end{equation}

Figure 6.16: Regioselective Ring Opening of Malic Acid Anhydrides

This approach was developed further by the same group and extended to general esters of \(\alpha\)-hydroxyacids \cite{97}. The characteristic step of this procedure is the C-acylation reaction of a malonic ester with an activated ester of an O-protected (i.e. O-acylated) \(\alpha\)-hydroxyacid. The activation of \(\alpha\)-aminoacids by way of the corresponding N-succinimidyl ester is well-known in the context of peptide syntheses \cite{98}. Mitsos and coworkers applied this activation method successfully to \(\alpha\)-acetoxyacids instead of using the acid chlorides like Anschütz. N-hydroxysuccinimide was condensed to the protected hydroxyacid (cf. Fig. 6.17 \(a\)) in the presence of 1 equivalent DCC. The reaction yields are more then satis-
6.2. SYNTHESIS OF 3-ACYLTETRONIC ACIDS

fying and the activated esters b are stable solids, which could be used without further purification. These compounds were subsequently reacted with the anion of an active methylene compound (i.e. a β-ketoester) to give a C-acylation product c. This cyclized readily upon deprotection of the hydroxy group under basic conditions to the 3-acylated tetronic acid.

![Chemical structure of 3-acyl tetronic acids]

Figure 6.17: Cyclization of activated Esters of α-Hydroxyacids

6.2.6 Synthesis of HIV-1 protease inhibitors

Mitra and coworkers proposed in 1997 a preparation method for 3-acyl-5-hydroxymethyltetronic acids with a long C-chain in the alkanoyl moiety. Their work was inspired by the discovery of six new homologues of the upper-mentioned tetronic acids by Roggo et al. [99, 100]. The total syntheses of this natural products are of special interest due to their biological activities (HIV-1 protease inhibitors).

They chose diphenylmalonate as starting material, whose anion was alkylated with allyl bromide in a first step. The double-bond was epoxidated by the action of m-chloroperbenzoic acid (m-CPBA). Palladium catalyzed hydrogenolysis afforded the corresponding epoxydicarboxylic acid (Fig. 6.18 d), which was then treated with trifluoroacetic acid followed by acetic anhydride to cyclize and acetylate, respectively, to 3-carboxy-5-acetoxyethyl-γ-butyrolactone e. The C-acylation was carried out by the condensation of the magnesium salt of e with
imidazolyltetradecanone under mild conditions. The acylation product was obtained as a diastereomeric mixture. The introduction of the carbonyl group was effected by the reaction sequence phenylselenation-oxidative elimination. Later, the acetyl group was removed by acidic hydrolysis to give the 5-hydroxymethyl-3-tetradecanoyltetronic acid with 7.9% overall yield.

Applying this protocol several analogs of $h$ are to be synthesized. Appropriate functionality in the long side-chain could lead to interesting applications concerning HIV pharmaceutical research.

6.2.7 Discussion

This summary of preparation protocols reflects the scientific work of almost one century. Starting with Benary’s and Anschütz’ first successful attempts in the
early 1900’s the way ends in the new millenium. The organic chemists are nowadays enabled to synthesize a huge variety of 3-acylated tetronic acid derivatives even in complicated total syntheses. Each particular method has its own peculiarities, so that one can state, that even the state-of-the-art methods give the desired species in only good but not very good yields.

In general, the protocols of Benary and Lacey have been the widely used synthetic procedures until now. Especially the more sophisticated recipes - in particular the use of acyl-Meldrum’s acids as precursors for the appropriate β-ketoesters and TBAF/THF as a very mild cyclization reagent - have led to versatile applications, culminating in the high-fidelity syntheses of Tetronasin and γ-methyl-α-nonanoyl tetronic acid as a prostaglandine precursor. Also the one-pot acylation procedure proposed by Yoshii in 1986 represents a well-developed method with good to excellent yields for - perhaps - industrial applications, provided, that the starting materials are easily available.

### 6.3 Synthesis of 3-Acylthiotetronic Acids

In general, 3-acylthiotetronic acids were less examined than 3-acyltetronic acids. The first descendants of thiotetronic acids, such as 4-hydroxy-2-oxo-2,5-dihydrothiophene-3-carbonitrile and 4-hydroxy-2-oxo-2,5-dihydrothiophene-3-carboxamide (Fig. 6.19), were described by Benary [101].

![Figure 6.19: First Descendants of Thiotetronic Acids](image)

#### 6.3.1 Survey over Synthetic Procedures and Applications

The first 3-acylthiotetronic acid (ethyl 4-hydroxy-2-oxo-2,5-dihydrothiophene-3-carboxylate) was synthesized by Benary three years later by adding (S)-acetylthioglycolic chloride to the sodium salt of diethyl malonate [102] (Fig. 6.20). After extracting with sodium carbonate solution, adding concentrated sodium lye and
finally acidifying, the product precipitated. Recrystallization from ethanol gave the product as colourless needles. The yield was not stated.

\[
\begin{align*}
\text{O}_3\text{S} & \quad \text{Cl} \\
\text{O} & \quad \text{O} \\
\text{S} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{Na}^+ &
\end{align*}
\]

Figure 6.20: Synthesis of Ethyl 4-Hydroxy-2-oxo-2,5-dihydrothiophene-3-carboxylate

3-Acetylthiotetronic acid was synthesized in an analogous way, just by adding the upper-mentioned chloride to the sodium salt of ethyl acetoacetate (Fig. 6.21). Colourless needles were collected after recrystallisation from ethanol with a melting point of 86-88 °C. The yield was not stated.

\((S)\)-Acetylthioglycolyl chloride is available by adding acetylchloride to thio-glycolic acid, followed by the chlorination of the resulting S-acetylthioglycolic acid via phosphorous pentachloride or thionylchloride.

By treating the 3-acetylthiotetronic acid with phenylhydrazine, 3-(2-phenyl-hydrazi neethyl)thiotetronic acid was collected as pale yellow needles with a melting point of 173-174 °C (Fig. 6.22).

3-Acetylthiotetronic acid, synthesized by an analogous way as Benary’s with a yield of 36 %, were condensed by O’Mant with aromatic aldehydes under either acidic or basic conditions in a Knoevenagel-Condensation [103] to give 5-arylidene compounds \((I)\) (Fig. 6.23). The acid-catalyzed reaction with dry hydrogen chloride gas gave around 48 % of the product, the base-catalyzed reaction around 34 %. The yields depend on the substituents, but it seems, that the reaction in an acidic medium gave higher yields. It also coupled readily with diazonium salts in
6.3. SYNTHESIS OF 3-ACYLTHIOTETRONIC ACIDS

Figure 6.21: Synthesis of 3-Acetylthiotetronic Acid

Figure 6.22: Synthesis of 3-(2-Phenylhydrazineethyl)thiotetronic Acid
CHAPTER 6. SYNTHETIC STRATEGIES

weak basic media to yield the 5-azo compounds (II). Furthermore, it condensed with thioglycolic acid in the presence of dry hydrogen chloride at -10 °C (III).

![ реакции 3-ацилтиотетреноидов O'Mant](image)

Figure 6.23: Reactions of 3-Acetylthiotetronic Acids by O'Mant

By heating 5-benzyl-2,5-dihydro-4-pyrrolidino-2-thiophene with dioxane and hydrochloric acid for 1h, 5-benzyl-2,5-dihydro-4-hydroxy-2-thiophene was collected as colourless crystals with a yield of 63 % and a melting point of 138 °C (Fig. 6.24) [104]. Heating this compound at 90 °C with acetylchloride and SnCl₄, extracting with sodium bicarbonate solution and acidifying gave 80 % of 5-benzyl-3-acetylthiotetronic acid as colourless crystals with a melting point of 140 °C. This was reduced to 5-benzyl-3-ethylthiotetronic acid by adding of sodium cyanoborhydride to a suspension in acetic acid. The product was obtained as a colourless oil (bp. 210 °C/0.1 Torr) with a yield of 80 %.

The α-thiotetronic acid (Z)-ethyl 2-(4-hydroxy-5-oxothiophen-2(5H)-ylidene)-acetate (Fig. 6.25) is transformed in an acid-catalyzed reaction with amines into oxo amides [105], whereas the reaction with benzylamine gave higher yields (80 %) than with methylamine (65 %). The reaction with aniline provided a α-
thiotetronic acid amide as a by-product.

Furthermore, alkylation of 3-acetylthiotetronic acid in THF with various allyl or alkyl halogenides in the presence of sodium hexamethyldisilane (NaHMDS) is possible (Fig. 6.26) [10]. One conjugated enamide derivative was also prepared by condensing the acid with dimethyl formamide diethyl acetal in toluene at 100 °C. More precise statements were not given.

Decarboxylation of 3-acyltetronic acids in 70 % trifluoroacetic acid yielded thiotetronic acids [106], as shown in Fig. 6.27. Acylation of this compound with acetyl chloride at room temperature in the presence of triethylamine gave rise to mixtures of O-acyl derivatives, which isomerized to 3-acetyl derivatives by treating with 4-N,N-dimethylaminopyridine (DMAP) or acetone cyanohydrin at room temperature in toluene. The product was transposed with allylamine and benzylamine into enaminodiketones (yield 75-90 %).

### 6.3.2 Discussion

Only one way of synthesizing 3-acetylthiotetronic acid has settled down until now. This is the one of Benary, which is simultaneously the only way made
Figure 6.25: Reactions of (Z)-Ethyl 2-(4-Hydroxy-5-Oxothiophen-2(5H)-Ylide)acetate with Amines

Figure 6.26: Reactions of 3-Acetylthiotetronic Acids by Sakaya et al. [10]
6.3. SYNTHESIS OF 3-ACYLTHIOTETRONIC ACIDS

Figure 6.27: Syntheses and Reactions of 3-Acylthiotetronic Acids by Budnikova and Rubinov [106]
by acyclic compounds. One other way describes the acylation of thiotetronic acids. They can finally be used for a variety of reactions, like the condensations with diazonium salts to 5-azo compounds or with benzaldehydes to 5-ylidene compounds, what is of significant importance with regard to medicinical products. Also the reactions with amines to oxo amides, or the alkylation with alkyl halides have been well established. The reactions with allylamines and benzylamines into enaminodiketones came out to be important to make NMR spectroscopical studies. In general, 3-acylthiotetronic acids were not as intensively studied as their oxo-relatives in the past. But it is foreseeable, that this will change in future, because these compounds are very interesting to examine, especially due to their different geometry.
3-Acyltetronic acids and 3-Acylthiotetronic acids appear in four enolic forms with two \textit{exo}-cyclic and two \textit{endo}-cyclic C=C-double bonds, respectively. In solution they show two ”internal” tautomers and a slower changing ”external” tautomeric pair. The latter one exhibits splitted signals by $^1$H-NMR and $^{13}$C-NMR spectroscopy, respectively. Even if the authors were not always in agreement in the past due to different interpretation of assignments, one can conclude, that the ”internal” tautomer next to the ring oxygen predominates. Molecular modeling in the gas-phase gave the result, that \textit{endo}-cyclic double bonds are less stable than \textit{exo}-cyclic double bonds, the form with the enolic hydrogen attached to the lactonic carbonyl group turned out to be the most stable tautomer. Also calculations of infrared frequencies have been made; the assignment was supported by Raman-data. These results are partially in consensus with the NMR spectroscopic results. By infrared spectroscopic measurements it could be shown, that $\alpha$-acetyltetronic acid is less influenced by dissolving and that the lactone-carbonyl group does not take part in intermolecular hydrogen-bond formation in the solid state. It could be stated, that the possibility of $\alpha$-acetyltetronic acid to form strong intramolecular hydrogen-bonding leads to a certain insensitivity to environmental changes.

Today, a wide variety of synthetic ways yielding 3-acyltetronic acid derivatives is known, whereas the amount of synthetic methods of synthesizing 3-acyltetronic acids surpasses those of 3-acylthiotetronic acids. For the latter ones, only some ways have been employed, in which the Knoevenagel-Condensation of 3-acetylthiotetronic acid with benzaldehyde derivatives is the most important
one, yielding biologically active products. The most significant synthetic strategies for 3-acyltetronic acids are the Dieckmann-type cyclization of acetoacetates, the Friedel-Crafts-Acylation and Fries-Rearrangement of 3-unsubstituted tetronic acids, as well as 1,3-dipolar cycloaddition of nitrile oxides to enamines.

The synthetic methods have been permanently improved in the past, especially due to biological applications. Since the biological activity of a substance does not imply possible medicinal applications \textit{a priori}, the product pallet has to be extended. Therefore, synthetic efforts are necessary to prepare tetronic acid derivatives, which can be used as human therapeutics.
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Part III

Appendices
Appendix A

Acknowledgements

Jan Philipp Hofmann and Markus Langsdorf like to thank their supervisor Prof. Fritz Duus for plenty of fruitful discussions and support in any case and under any circumstances. Moreover, they appreciate very much the services of the Roskilde Universitetsbibliotek for providing the necessary informations. The authors have been supported by the ERASMUS programme and therefore wish to express their gratitude. Jan Philipp Hofmann is very grateful for the support by the German National Academic Foundation.
Appendix B

Statutory Declaration

The authors - namely Jan Philipp Hofmann and Markus Langsdorf - declare hereby, that the contents of the present thesis are based only on the material listed in the bibliography and on own considerations. This essay has neither been handed over to other institutions before, nor has it been published before.

Jan Philipp Hofmann

Markus Langsdorf

DK-4000 Roskilde, June the 14th 2005.