STUDIES IN THE UNSATURATED LACTONE GROUP

by

Jack R. Plimmer, B.A.(T.C.D.).

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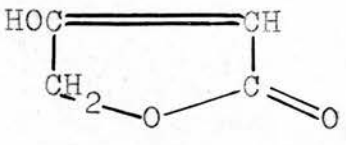
C O N T E N T S.

U.V. Absorption spectra: Page

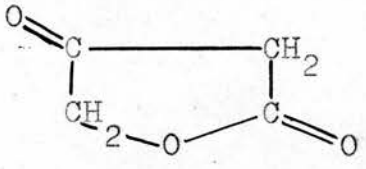
INTRODUCTION

INTRODUCTION.

The unsaturated lactones chosen for study in this thesis are mainly tetronic acids or their derivatives. Tetronic acid is a γ-lactone of γ-hydroxy acetoacetic acid whose structure may be written in the enolic form [I] or in the ketonic form [II]:



[I]



[II]

Written as the former it is the γ-lactone of β-γ-dihydroxy crotonic acid and this form is of greater importance chemically, but the system possesses characteristics distinct from those of the open chain compounds to which it bears a formal resemblance.

Tetronic acids occur naturally, mainly as mould metabolites, and some account of the naturally occurring compounds is given later. In this introduction it is proposed to review the preparation, chemical and some physical properties of the tetronic acids in order to show the relationship of the experimental work undertaken to previous work in the above fields and its relevance to structural studies.

THE CONSTITUTION OF THE TETRONIC ACIDS.

In 1879 Demarçay (Compt.rend.,1879,88,126) first prepared ∝-methyl tetronic acid (named tetric or tetrinic acid in the literature previous to 1896) and some homologous compounds by bromination of ∝-mono alkylated acetoacetic esters followed by pyrolysis. For ∝-methyl tetronic acid he gave the incorrect formula $3C_4H_4O_2+H_2O$ ($=C_{12}H_{17}O_7$). He also described (Compt.rend., 1879,88,289) the preparation of a compound, which he named "oxytetric acid", and some of its homologues. These compounds he obtained by action of alcoholic potassium hydroxide on the 3:3-dibromo compounds obtained by action of bromine on ∝-monoalkylated aceto-acetic esters. The formation of the "oxytetric acids", however, was shown to occur by an entirely different route to that of tetronic acids and M. Conrad (Ber., 1899,32,1005) showed that "oxytetric acid" was methyl fumaric acid arising by the series of reactions:-

$$X_2.CH.CO.CHR'.CO_2R \xrightarrow{KOH} CHO.CO.CHR'.CO_2R$$
$$\longrightarrow CHO.C(OH)=CR'.CO_2R \longrightarrow HO_2C.CH=CR'.CO_2R$$

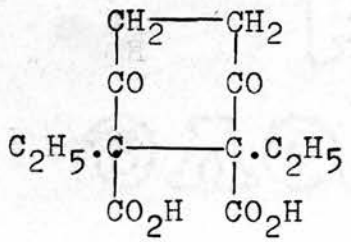
W. Pavlov (J.Russ.Phys.Chem.Soc.,1883,[I],274 abstracted in Ber.,1883,16,1870) gave the correct molecular formula for ∝-methyl tetronic acid, which he, however, expressed as being derived from ∝-monobromo-

∝-methyl acetoacetic ester by loss of ethyl bromide according to the equation:-

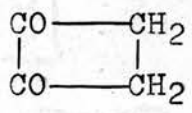
$$CH_3.CO.C(CH_2R)Br.CO_2Et \xrightarrow{-EtBr} CH_3.CO.C(=CHR).CO_2Et.$$

(R=H in the case of ∝-methyl tetronic acid).

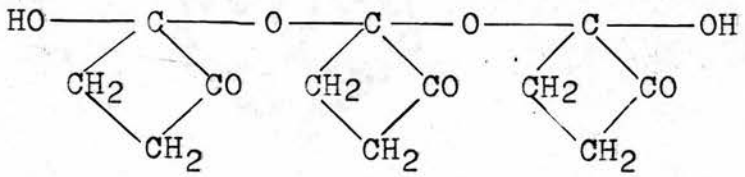
The compounds were regarded by him as ∝-acetylated acrylic acids. At the same time, Wedel (Ann.,1883,219, 71), who appeared to be unaware of Demarçay's work, synthesised ∝-ethyl tetronic acid and determined the correct empirical formula but the properties of the compound led him to believe that it had formula [I], a derivative of succinoyl succinic acid, and that the empirical formula ($C_6H_8O_3$) should be doubled to give the true formula.



[I]



[II]

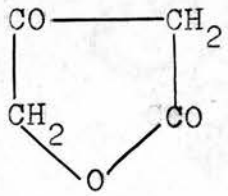


[III]

Independently R. Fittig (Ber.,1883,16,1939) discussed structure [II] advanced by Demarçay (Ann.Chim.Phys., 1880,[5],20,433) for ∝-methyl tetronic acid (or in the hydrated form [III]) but found that the compound was anhydrous and determined the correct empirical formula. He also found by analysis of the silver salt that it was a monobasic acid which refuted the opinion of Wedel that the formula should be doubled.

The first correct view of the structure of tetronic acid was put forward by A. Michael (J.Prakt.Chem.,1888, 37,502) in a review in which he discussed the reactivity of acetoacetic ester towards halogens and reinterpreted the work of Demarçay (loc.cit.). Michael suggested that ∝-methyl acetoacetic ester undergoes γ-bromination and that the γ-bromo compound by the action of alkali in the cold gives a lactone:-

$$CH_2Br.CO.C(CH_3)H.CO_2Et \xrightarrow{NaOH} CH_2Br.CO.C(CH_3)H.CO_2Na + EtOH$$

$$\longrightarrow$$  + NaBr

Therefore ∝-methyl tetronic acid may be regarded as the lactone of γ-hydroxy-∝-methyl acetoacetic acid.

The appearance of Michael's work prompted publication of an account of the research of R. Moscheles and H. Cornelius (Ber.,1888,21,2603) for whom the theory provided a satisfactory interpretation of the reactions which they had investigated.

In order to decide between the formulae of Wedel (loc.cit.) and that of Pavlov (loc.cit.) they examined first the properties of the 'ethers' of succinoyl succinic acid and compared these with the ethers of ∝-methyl and ∝-ethyl tetronic acids. (The term 'ether' was applied to both ether and ester and the ethers of tetronic acids were at first regarded simply as esters). They found that in spite of physical resemblances the two types differed chemically and, whereas the former were readily hydrolysed by alkali in the cold, the latter were resistant to alkali and were only hydrolysed by acid.

Attempts to synthesise ∝-methyl tetronic acid from the sodio derivative of succinoyl succinic ester failed. In view of these results, Pavlov's formulation (loc.cit.) of ∝-methyl tetronic acid as ∝-acetylacrylic acid was considered, but the ethers of tetronic acids showed no formation of a phenylhydrazone with phenylhydrazine as would be expected if an acetyl group were present.

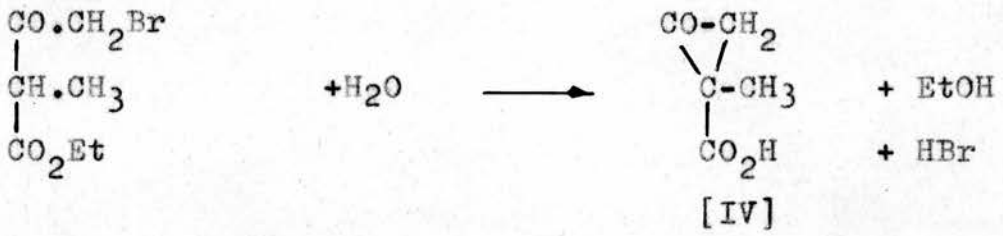
∝-Benzoylpropionic acid would give no tetronic acid-like material showing that the γ-hydrogen atom was

was involved in formation of these compounds. Likewise from ∝∝-dimethyl acetoacetic ester no tetronic acid like material was obtained (cf.Conrad and Gast,Ber.,1898,31, 2726) and from this the presence of an ∝-hydrogen atom also appeared necessary.

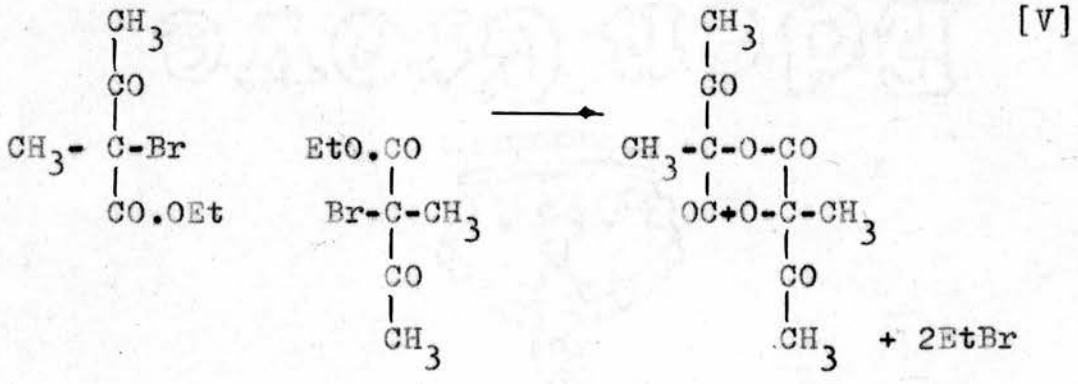
Their work concluded with an attempt to allot the three oxygen atoms to their proper functions. As two were thought to be involved in formation of a carboxyl group, when it was found that the ether or "ester" gave no phenylhydrazone it was presumed that third oxygen atom could not be ketonic. However, it was realised that the acidity of compound could not lie in a carboxyl group as the so called acid chloride, "tetrinic acid chloride" of Demarcay, unlike a true acid chloride was very resistant to alkali. The acid character of the compound must then be due to a phenolic hydroxyl group derived from a >CH group lying between two carbonyl groups. Etherification was then considered to be made possible by a shift of >CH-CO-to>C=C(OH)- and the presence of a ketonic group in the free acid was confirmed by the formation of a phenylhydrazone.

The same authors (Ber.,1889,22,243) established the true formula of ∝-ethyltetronic acid as $C_6H_8O_3$ by determination of its molecular weight by lowering of freezing point.

L. Wolff (Ann.,1890,260,79) studied the reactions of some unsaturated lactones and made some observations on ∝-methyl tetronic acid, suggesting [IV] as the formula because the strongly acidic nature of this compound forced him to adopt the belief that a carboxyl group must be present.



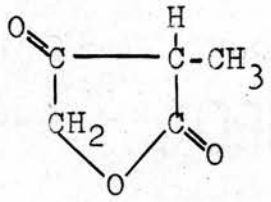
A further structure [V] was advanced by J. U. Nef (Ann.,1891,266,92) who considered that a lactide type of compound arose by loss of ethyl bromide between two molecules of ∝-methyl-∝-bromoacetoacetate:-



[V]

In a paper revising his former views (loc.cit), Wolff (Ann.,1895,288,1) supported the formula given by

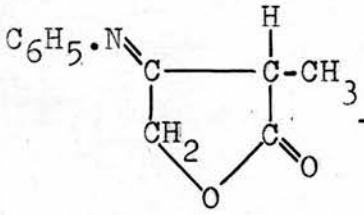
Michael (loc.cit.) and substantiated this formula experimentally by alkaline and neutral degradation of ∝-methyl tetronic acid, which took place in the manner indicated:



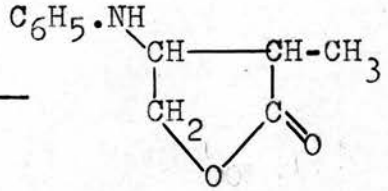
$\xrightarrow{Ba(OH)_2}$ $CH_2OH.CO_2Et + C_2H_5.CO_2H$

$\xrightarrow[H_2O]{200°}$ $CH_2OH.CO.C_2H_5$ (ethyl ketol)

By reduction of the anilide of ∝-methyl tetronic acid he was able to obtain ∝-methyl-β-anilido-γ-butyrolactone which on acid treatment followed by reaction with aqueous baryta gave the barium salt of a substituted γ-hydroxy-butyric acid, thus illustrating the relationship of the parent compound to γ-butyrolactone.

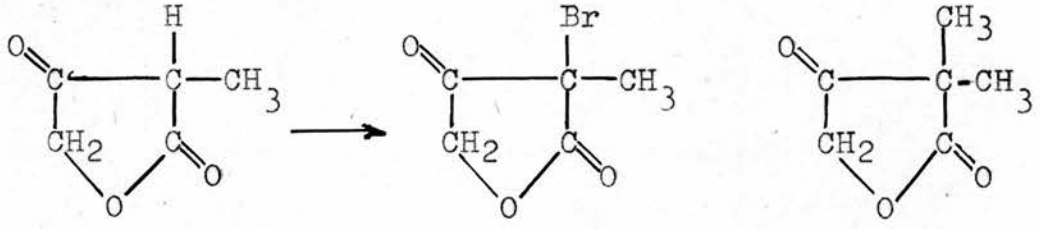


$\xrightarrow{2H}$



$\xrightarrow[Ba(OH)_2]{HCl,\ then}$ $(CH_2OH.CHOH.CHMe.CO_2)_2Ba$

Confirmation of the view that the acidity of ∝-methyl tetronic acid was due to a possible enolic form was obtained by bromination to give a non-acidic monobromo compound [VI].



[VI] [VII]

Tetronic acid itself was prepared in 1896 by Wolff and Schwabe (Ann.,1896,291,231) as Wolff had realised that if the formula put forward for ∝-methyl tetronic acid was correct the parent member of the series was still unknown, thus further confirmation of the structure was obtained.

The position was reviewed in a paper by M. Conrad and R. Gast (loc.cit.) who accepted the formula of Wolff and discussed the ketonic and enolic forms of tetronic acid. They prepared the lactone of ∝∝-dimethyl -γ-hydroxy-β-keto-butyric acid [VII] and showed that it was not a tetronic acid. In physical properties it differed from the tetronic acids, whereas ethyl ∝-methyl and ∝∝-dimethyl acetoacetate are very similar

to the unsubstituted compound. From this point of view they thought that α-methyl-β-hydroxy crotonolactone would be distinguishable by boiling point from α-methyl -β-keto-butyrolactone (which in their opinion was unlikely to exist). Nevertheless, they considered it noteworthy that keto and enol forms of acetoacetic ester could not be separated by fractional distillation.

The correct structure for tetronic acid as the γ-lactone of γ-hydroxyacetoacetic acid was thus established. The question of its ketonic or enolic nature which has been a subject of more recent studies will be reviewed in a separate section (p.11).

THE CURRENT VIEW OF THE STRUCTURE OF TETRONIC ACID.

W. D. Kumler has measured the dissociation constants of tetronic acid and several related compounds(J.Am.Chem, Soc.,1938,60,859) and his values are given in Table I.

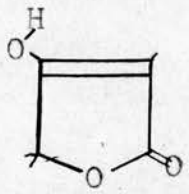
Table I

	pKa
∝-Chlorotetronic acid	2.13±0.013
∝-Bromotetronic acid	2.23±0.005
∝-Iodotetronic acid	2.31±0.005
Tetronic acid	3.76±0.003
∝-Hydroxytetronic acid	4.37±0.02
Ethyl ∝-iodoacetoacetate	7.0
Ethyl acetoacetate	10.7

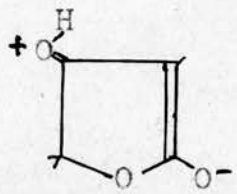
By analysis of the salts of tetronic acid he has shown that the enolic hydroxyl group is responsible for its strong acidity (pK_a 3.76±0.003). Later (J.Am.Chem.Soc., 1940,62,3292) he measured the dipole moments of tetronic acid and some substituted tetronic acids. From the measured dipole moment of tetronic acid in dioxan (4.72D) he drew several inferences concerning the structure and forms participating in resonance, the evidence indicating formula (I). To account for the high dipole moment the participation of a form with charge separation appeared necessary, such as (II),

and to bring the measured dipole moment into agreement with the calculated figure, Kumler proposed a fixation of the hydrogen atom of the enolic group over the ∝-carbon atom as shown [I].

The acid strength of tetronic acids was explained by Kumler as due to the stabilisation of the ion by resonance forms. It is a much stronger acid than the corresponding open chain β-keto-esters such as ethyl acetoacetate and the open chain β-diketones and Kumler compares the participating resonance forms [see diagrams III-XII]. β-Ketonic esters possess a third resonance form which stabilises the undissociated acid relative to the ionic form, due to an unfavourable charge distribution in the latter, thus rendering the acid weaker, whereas β-diketones do not possess this form. In tetronic acids, the participation of the third resonating form in the ion and in the acid would be excluded by the presence of two double bonds in the ring, in consequence the acidic strengths should be very close to those of β-diketones (W. D. Kumler, J.Am.Chem.Soc., 1940,62,3292 gives values: tetronic acid K_a 1.7×10^{-4} acetyl acetone K_a 1.3×10^{-5}). But F. S. Fawcett (Chem. Reviews, 1950,47,250) has discussed compounds in which the β-diketonic system, by inclusion in a cyclic system, is fixed in space so that hydrogen bonding, which tends to diminish acidity in compounds such as acetylacetone,

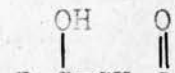
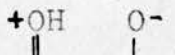


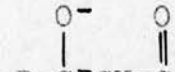
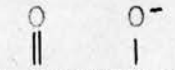
[I]



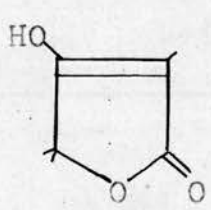
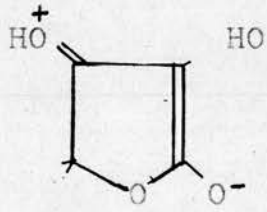
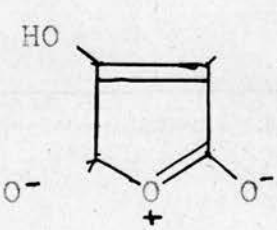
[II]

β-Diketone:

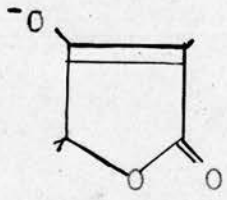
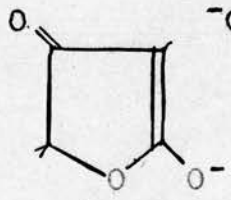
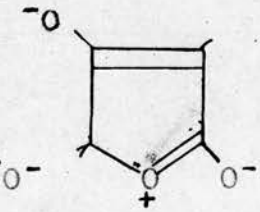
Enol  [III]  [IV]

Ion  [V]  [VI]

Tetronic acid:

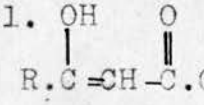
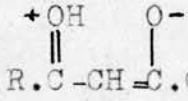
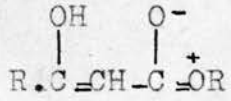
Enol   

[VII] [VIII] [IX]

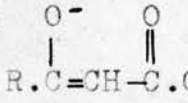
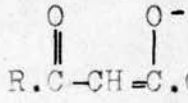
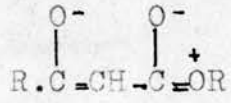
Ion   

[X] [XI] [XII]

β-Ketonic ester:

Enol.   

[XII] [XIV] [XV]

Ion.   

[XVI] [XVII] [XVIII]

is absent. This argument has been invoked to explain the acidity of 5:5-dimethylcyclohexane-1:3-dione (pK_a 5.25, G. Schwarzenbach and E. Felder, Helv.Chim.Acta,1944,44, 1701) in which hydrogen bonding cannot occur (G. W. Wheland, 'Advanced Organic Chemistry', 2nd. edition, John Wiley, New York p.616) and in combination with ring strain to explain the acidic strength (pK_a 2.8) of the acidic dimer of methyl ketene (R. B. Woodward and G. Small, J.Am.Chem.Soc.,1950,72,1301). However, C. K. Ingold ('Structure and Mechanism in Organic Chemistry' G. Bell, London 1953,p.79) has suggested that the flexibility of the 5:5-dimethylcyclohexane-1:3-dione ring may permit some degree of hydrogen bonding. This latter view might be criticised on the grounds that calculation of the distance in a planar mesomeric HO-C=C-C=O system between the carbonyl and hydroxyl groups shows that this distance ca. 4A. is excessively large for hydrogen bonding. Further information concerning the structure of the tetronic acids is available from ultra-violet and infra-red spectral evidence. J. T. Edsall and E. L. Sagall (J.Am.Chem.Soc., 1943,65,1312) made the first study of the vibrational spectrum of tetronic acid from Raman spectra and found that it possessed an intense line in the region of 1727 $cm.^{-1}$ not observed in the spectrum of the ion, a line at 1680 $cm.^{-1}$ weak in the acid, but intense on ionisation

and an intense line at 1580 $cm.^{-1}$ which was not affected by ionisation.

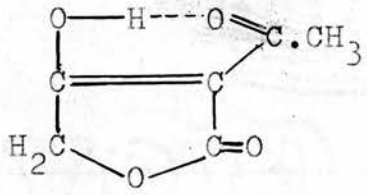
They made similar observations to those of W. D. Kumler (loc.cit.) concerning the acidic strength of these compounds, namely that resonance in the anion between two forms of approximately equivalent energy such as [X] and [XI] would stabilise the anion relative to the conjugate acid, where the second form in resonance must be dipolar as [VIII] and of larger internal energy than [VII].

The infra-red spectrum of some substances related to tetronic acid have been described by I. F. Trotter, H. W. Thompson and E. Wokes (Biochem.J.,1948,42,601), whose studies included α-hydroxytetronic acid and ascorbic acid, and, more recently, by L. A. Duncanson (J.Chem.Soc.,1953,1207).

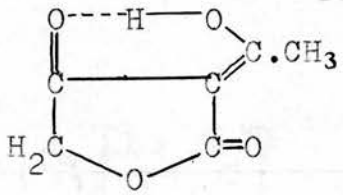
Duncanson concludes that in some solvents an equilibrium between ketonic and enolic forms exists in which the ketonic form predominates.

In the solid state the lactone carbonyl frequency of tetronic acids, with the exception of α-acetyl tetronic acid, was much lower than would be expected for five membered ring lactones, (J. F. Grove and H. A. Willis, J.Chem.Soc.,1951,877) which was interpreted to mean that in the solids strong intermolecular hydrogen bonding occurred.

∝-Acetyl tetronic acid showed bands at 3080,1675 and 1600 $cm.^{-1}$ which were assigned respectively to vibrations involving OH stretching, >C=O stretching and -C=C- stretching in the -C(OH)=C.CO- system. In addition a band at 1758 $cm.^{-1}$ was assigned to the lactone carbonyl group, so that in this case the lactone carbonyl group does not take part in hydrogen bond formation in the solid state but the acetyl carbonyl group presumably forms an intramolecular hydrogen bond as in [XIX] and [XX].



[XIX]



[XX]

Tetronic acids and ∝-alkyl tetronic acids on dissolving in chloroform showed a shift to higher frequencies of bands assigned to C=C stretching, consistent with the formulation of tetronic acids as lactones of ɣ-hydroxy-β-keto-carboxylic acids in the enolic form, but weak bands at frequencies higher than 1750 $cm.^{-1}$ suggest that a keto-enol equilibrium is present with the enolic form predominating.

By changing the solvent it was hoped that the equilibrium could be altered to show a considerable amount of ketonic form, accordingly measurements were made in

ethylene dichloride on γ-methyl tetronic acid and the lactone of β-hydroxy-β-(1-hydroxycyclohexyl) acrylic acid which showed bands near 1800 and 1760 $cm.^{-1}$ assigned to saturated five membered ring lactone and saturated five membered ring ketone carbonyl groups respectively. This was taken to mean that in ethylene dichloride the ketonic forms of these acids predominate, and additional evidence was given by the almost complete disappearance of bands due to the C=C stretching frequency near 1630 $cm.^{-1}$. In the case of α-ethyl tetronic acid the same indications of the presence of a ketonic form were not observed, suggesting stabilisation of the enolic form by an α-alkyl group.

The author measured the ultra violet absorption spectra of α-ethyl tetronic acid and γ-methyl tetronic acid and his results will be discussed later.

Duncanson makes the following summary:

'(i) In the solid state, alkyltetronic acids have strong hydroxyl absorption bands in the range 2500-2700 $cm.^{-1}$, and strong double bond stretching bands near 1650-1700 $cm.^{-1}$ and 1565-1580 $cm.^{-1}$, due to the enol forms associated through strong inter-molecular hydrogen bonds.

(ii) Dilute solutions of alkyltetronic acids in chloroform containing a trace of alcohol show band near 1740 and 1630 $cm.^{-1}$ (1740 and 1675 $cm.^{-1}$ for α-substituted acids) corresponding to the monomeric enol forms.

(iii) γ-Alkyltetronic acids dissolved in ethylene dichloride have absorption bands near 1800 and 1760 $cm.^{-1}$ which correspond to the keto forms.

(iv) α-Acyltetronic acids do not show a marked change in the general pattern of their absorption spectra in passing from the solid state to solution. The last generalisation presumably applies to all tetronic acids in which the enolic hydroxyl group is able to form an intramolecular hydrogen bond with an oxygen atom. This class includes ascorbic and hydroxytetronic acids, which were found by I. F. Trotter et al. (loc.cit.) to have absorption maxima at 1750 $cm.^{-1}$ (lactone C=O) and 1650 $cm.^{-1}$ (C=C) in the solid state.'

Table II shows further determinations of values of the infra-red absorption frequencies of some alkyl substituted tetronic acids (W. Cocker et al., J.Chem.Soc., 1955, 588).

Table II

α-Methyl tetronic acid

In CH_2ClCH_2Cl	In $CHCl_3$
1788 $cm.^{-1}$	1751 $cm.^{-1}$
	1676 $cm.^{-1}$

Table II (contd.)

∝-γ-Dimethyl tetronic acid

In CH_2ClCH_2Cl	In $CHCl_3$	In Nujol
1756 $cm.^{-1}$	1738 $cm.^{-1}$	1725 $cm.^{-1}$
1690 $cm.^{-1}$	1673 $cm.^{-1}$	1664 $cm.^{-1}$
		2720 $cm.^{-1}$

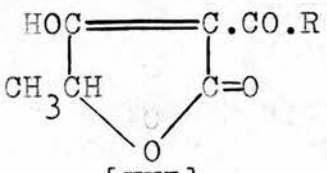
The ultra-violet spectrum of the tetronic acids was first studied by Japanese workers (J.Pharm.Soc. Japan, 1923,863) however, this paper, in Japanese, was not available.

In 1935 R. W. Herbert and E. L. Hirst (Biochem.J. 1935,39,1881) measured the absorption spectra of some substituted tetronic acids, which were obtained as mould metabolites from Penicillium Charlesii, and determined their relationship to the absorption spectrum of ascorbic acid. The chemistry of the metabolites from P. Charlesii will be considered later (p.56) but some of the features of their spectra and of the spectra of their derivatives are common to tetronic acids bearing similar substituents such as ∝-acetyl and ∝-ethyl tetronic

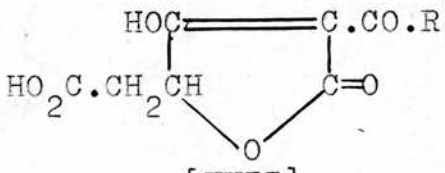
acids, which were also investigated by R. W. Herbert and E. L. Hirst.

The characteristic features of the spectra were, for ∝-ethyl tetronic acid in aqueous solution, a single band with $\lambda_{max.}$ 2580A. ($\varepsilon_{max.}$ 12,000) in acidified aqueous solution this shifted to $\lambda_{max.}$ 2330A. ($\varepsilon_{max.}$ 12,000) but in alkaline solution $\lambda_{max.}$ remained at 2580A. whilst $\varepsilon_{max.}$ increased to 18,000. In the case of ∝-acetyl tetronic acid the introduction of an ∝-carbonyl group modified the spectrum so that intense absorption bands situated at 2650A. and at 2300A. ($\varepsilon_{max.}$ 15,000 for both) were observed and with these showed no appreciable change in wavelength when aqueous acid or aqueous alkaline solutions were used in place of pure water.

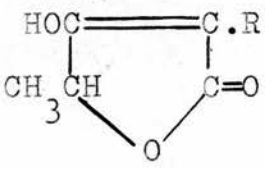
The mould metabolites investigated were of the general types [XXI] and [XXII] (and their reduction products are given by [XXIII] and [XXIV]).



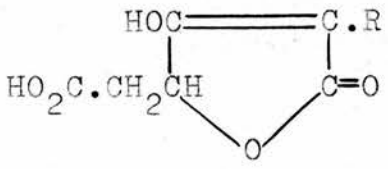
[XXI]



[XXII]



[XXIII]



[XXIV]

[XXI] $R = -(CH_2)_2CO_2H$ Carolinic acid

$R = -(CH_2)_2CH_2OH$ * Carolic acid

[XXII] $R - -(CH_2)_2CH_3$ Carlosic acid

$R - -(CH_2)_2CH_2OH$ * Carlic acid

[XXIII] $R - -(CH_2)_3CO_2H$ Tetrahydrocarolinic acid

$R - -(CH_2)_3CH_2OH$ Tetrahydrocarolic acid

[XXIV] $R - -(CH_2)_3CH_3$ Tetrahydrocarlosic acid

$R - -(CH_2)_3CH_2OH$ Tetrahydrocarlic acid

* hydrated form

It was found that the four metabolic acids showed in aqueous solution two strong bands of similar position and intensities to those of ∝-acetyl tetronic acid and on reduction these acids gave tetrahydro derivatives which showed singly banded spectra similar in position and intensity to those of ∝-ethyl tetronic acid. The values obtained by R. W. Herbert and E. L. Hirst are given in Table III.

These observations confirm the views of P. W. Clutterbuck, H. Raistrick and F. Reuter (Biochem.J. 1934,28,94; 1935,29,300,871,1300) on the formulation of the acids as tetronic acid derivatives. However, R. W. Herbert and E. L. Hirst found that whereas carolinic and carlosic acids had similar spectra in aqueous and alkaline solutions carlic and carlosic acids showed in alcoholic solution a single absorption band.

(Carolic acid: $\lambda_{max.}$ 2720A., $\varepsilon_{max.}$ 15,000; carlic acid $\lambda_{max.}$ 2700A., $\varepsilon_{max.}$ 16,500) indicating that some modification of the absorbing system had occurred. This will be discussed later in connection with the postulated structures for these acids (p. 65).

Table III (R. W. Herbert and E. L. Hirst, Biochem.J., 1935,39,1881)

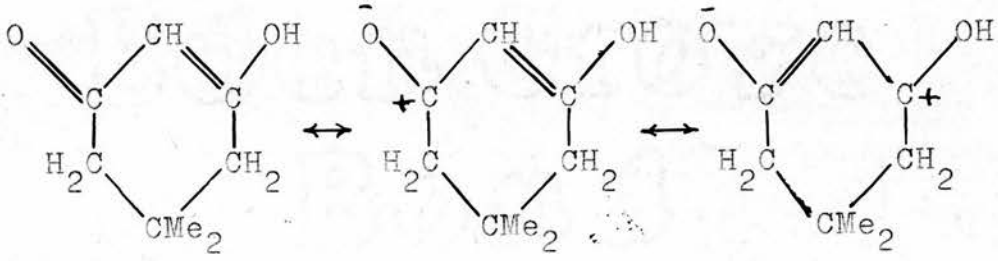
(i) In water	$\varepsilon_{max.}$	λ	$\varepsilon_{min.}$	λ	$\varepsilon_{max.}$	λ
∝-Acetyl tetronic acid	15,000	265	9000	243	15,000	230
Carolic acid	13,500	265	7500	245	13,000	230
Carlic acid	16,400	266	7500	245	14,200	230
Carolinic acid	13,800	265	8600	242	12,600	230
Carlosic acid	14,000	265	7500	245	13,200	230
∝-Ethyl tetronic acid	12,000	258				
Tetrahydrocarolinic acid	11,500	252				
Tetrahydrocarlosic acid	9,000	252				
Tetrahydrocarlic acid	12,000	258				
Tetrahydrocarolic acid	12,500	257				
(ii) In acid solution (N/40 H_2SO_4)						
∝-Acetyl tetronic acid	15,000	265	9000	243	15,000	230
Carolic acid	14,000	268	6000	245	8,500	230
Carlic acid	14,200	266	6500	255	8,200	230
Carolinic acid	13,800	265	8600	242	12,600	230

Table III (contd.)

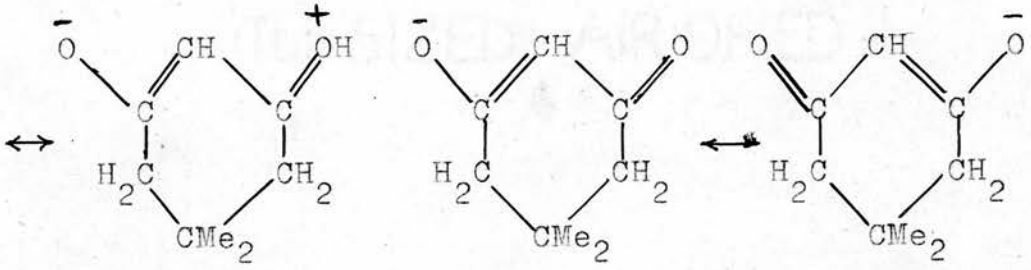
	$\varepsilon_{max.}$	λ	$\varepsilon_{min.}$	λ	$\varepsilon_{max.}$	λ
Carlosic acid	14,000	265	7500	245	13,200	230
∝-Ethyl tetronic acid	12,000	233				
Tetrahydrocarolinic acid	11,500	232				
Tetrahydrocarlosic acid	9,500	235				
Tetrahydrocarlic acid	12,000	234				
Tetrahydrocarolic acid	11,000	233				
(iii) <u>In Alkaline solution (Aqueous NaOH)</u>						
∝-Acetyl tetronic acid	15,000	263-5	8000	243	15,000	230
Carolic acid	13,500	265	7500	245	13,000	230
Carlic acid	16,400	266	7500	245	14,200	230
Carolinic acid	13,800	265	11000	244	14,000	230
Carlosic acid	15,000	265	8800	245	13,500	230
∝-Ethyl tetronic acid	18,000	258	3000	225		
Tetrahydrocarolinic acid	16,000	255-60	1600	220		
Tetrahydrocarlosic acid	19,000	260	3500	225		
Tetrahydrocarlic acid	19,000	258	4000	225		
Tetrahydrocarolic acid	17,000	258	4000	226		

The shift of the wavelength found in the case of γ-methyl tetronic acid on changing from aqueous acid solution ($\lambda_{max.}$ 2260A.) to aqueous alkaline solution ($\lambda_{max.}$ 2500A.) 240A. is parallelled in the case of

5:5-dimethylcyclohexane-1:3-dione where E. R. Blout, V. W. Eager and D. C. Silverman (J.Am.Chem.Soc.,1948, 68,566) found a similar concentration-dependent shift of 240A. ascribed to increasing ionisation. This was confirmed by measurements in acidic and basic solvents (λenol 2580A., λion 2820A.). The forms participating in resonance bear a formal analogy to those already put forward in the case of the tetronic acids.



enol



enol ionic forms

A later observation on the spectrum of ∝-hydroxy tetronic acid by H. Mahler and H. Lohr (Helv.Chim.Acta., 1938,21,485) showed the same characteristics as recorded by R. W. Herbert and E. L. Hirst for ascorbic acid, thus illustrating the relationship between these two compounds.

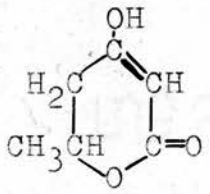
Hydroxytetronic acid (H. Mahler and H. Lohr, loc.cit.)

	$\lambda_{max.}$	log.ε
In ethanol	242	
In water ($0.5\ 10^{-3}$ molar)	246	3.87
In KCN ($0.3\ 10^{-3}$ molar)	262	4.10
Ascorbic acid (R. W. Herbert and E. L. Hirst, loc.cit.)		
N/10 solution in water	245	
In aq. acetate buffer (N/10) with a trace KCN. [pH5]	265	4.11

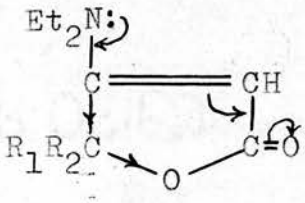
E. R. H. Jones and M. C. Whiting (J.Chem.Soc., 1949,1419) have given absorption maxima and intensities for several substituted tetronic acids and their ethers in alcoholic solution. From the correspondence between maxima and intensities for the acids and their enol ethers it was concluded that the acids existed mainly in the enolic form. (Table IV) The values observed by E. R. H. Jones and M. C. Whiting for the absorption maxima of the acids in ethanol are similar to those found by R. W. Herbert and E. L. Hirst (loc.cit.) when measurements were made in acidified aqueous solution and therefore correspond to the absorption maxima of undissociated enolic forms.

These authors concluded that whereas the δ-lactones of the type [XXV] showed little variation in light absorption properties from similar acyclic compounds,

the γ-lactones absorbed at much shorter wavelengths, a feature related to the unusual chemical stability of such γ-lactones. The direction of electronic effects responsible for the character of these compounds as envisaged by these authors are shown for the lactone of β-diethylamino-β-(1-hydroxycyclohexyl) acrylic acid [XXVI] but they have suggested that the effects would be less marked with systems possessing β-substituents with less mobile electron pairs such as NHPh or OMe



[XXV]

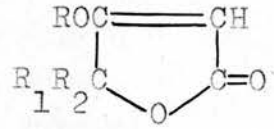


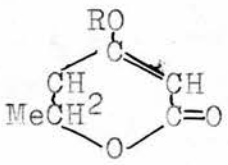
[XXVI]

It seems well established (W. D. Kumler, J.Am.Chem.Soc. 1938,60,859) (E. R. H. Jones and M. C. Whiting, J.Chem.Soc., 1949,1419) that tetronic acids exist in the solid state and in polar solvents as the enolic form. In some solvents, however, it would appear that an equilibrium mixture exists in which there is a considerable amount of ketonic form.

Ultra-violet measurements for γ-methyl tetronic acid and α-ethyl tetronic acid in acidified solution (R. W. Herbert and E. L. Hirst, loc.cit.) and in methylene dichloride (L. A. Duncanson, loc.cit.) are given in Table V.

Table IV (E. R. H. Jones and M. C. Whiting, loc.cit.)

A 

B 

			λ (mμ)	ε
A	R=H	$R_1R_2=(CH_2)_5$>	224	13,000
A	R=H	$R_1=R_2=CH_3$	223	13,500
A	R=H	$R_1=Pr, R_2=H$	223	13,500
A	$R=CH_3$	$R_1R_2=(CH_2)_5$>	221	15,500
	$CH_3CH=CH.C(OH)=CH.CO_2H$		280	6,500
	$CH_3CH=CH.C(OMe)=CH.CO_2H$		265	15,500
B	$R=CH_3$		234	17,000
B	R=H		239	12,000
			242	12,000
	* MeO.CMe=CH.COOH		234	13,500
A	R=OPh, $R_1R_2=(CH_2)_5$		223	13,000
			237*	11,000
	$(CH_2)_5$>C(OH)C(OPh)=CH.CO_2Me		218	21,500
			256	3,500
	$(CH_2)_5$>C(OH)C(OPh)=CH.CO_2H		220	16,000
			254	3,500

* (L.N.Owen, J.Chem.Soc., 1945, 385)

* Inflexion.

The figures are interpreted by Duncanson as showing that in both these solvents ∝-ethyl tetronic acid exists as the enolic form, but that the enolic form of γ-methyl tetronic acid is not present to any great extent in ethylene dichloride solution.

Table V. (L. A. Duncanson loc.cit.)

		$\lambda_{max.}$	log.ε
	∝-Ethyl tetronic acid		
I)	In ethylene dichloride (8.28×10^{-4}M.)	225	4.0
II)	In aqueous H_2SO_4	233	4.1
	γ-Methyl tetronic acid		
I)	In ethylene dichloride (11.1×10^{-4}M.)	219	2.9
II)	In aqueous H_2SO_4	226-7	4.2

(Values of R. W. Herbert and E. L. Hirst, loc.cit.)
(Cell length, 0.1cm. Slit width 2mm.)

The percentage of enolic form present in a solution of γ-methyl tetronic acid in benzene has been measured by B. Eistert (Lecture, Hamburg, Nov., 1951 quoted by G. Briegleb and W. Strohmeier, Angew.Chem.,1952,64,409) and this was found to be 69%. This is higher than might be expected from the findings of L. A. Duncanson (loc.cit.) whose measurements suggest that in ethylene dichloride only a very small percentage of enolic form is present and therefore in a less polar solvent such as benzene the amount of the enolic form might be expected to be

even lower.

A quantitative estimate can be made from the figures of Duncanson of the percentage of enolic form present in an ethylene dichloride solution of γ-methyl tetronic acid if we assume that the value of log.ε for a solution of the compound which is entirely in the enolic form is given by the value measured in aqueous sulphuric acid, (ε_{enol}).

Then if the percentage enol present in γ-methyl tetronic acid in ethylene dichloride solution is c_1 and ε_1 is the extinction coefficient measured in this solution.

Then:
$$\frac{c_1}{100} = \frac{\varepsilon_1}{\varepsilon_{enol}}$$

$$c_1 = \frac{100 \times 790}{15,900}$$

$$= \underline{ca}.5\%$$

The relative amount of the ketonic form at equilibrium is greatest in that solvent in which its relative solubility (S_K/S_E) is greatest (G. W. Wheland, "Advanced Organic Chemistry, Second edition, John Wiley, New York, p.607) and from an increase in the percentage of the less polar ketonic form would be expected as the polarity of the solvent decreases.

From measurements of infra-red spectra L. J. Bellamy L. Beecher (J.ChemSoc.,1954,4487) have shown that cyclohexane-1:3-diones at extreme dilution in non-polar

solvents exist only in the diketo form. The forces of intermolecular hydrogen bonding are of less account at such dilutions so that similar effects might be observed in solutions of tetronic acids in non-polar solvents at low concentrations such as those required for ultra-violet absorption measurements.

The question of keto-enol tautomerism is not a simple one and it requires much more data for any satisfactory treatment. The subject of such equilibrium in general has been reviewed by G. Briegleb and W. Strohmeier (loc.cit.) and these authors lay stress on the thermodynamic aspects of the subject and the importance of measurements of the equilibrium over a range of temperatures. In solvents, there is present a solvation effect and this must certainly be important in its effect on the equilibrium of tetronic acids in polar solvents. The measurements of L. J. Bellamy and L. Beecher (loc.cit.) on cyclohexane-1:3-diones show that accurate observations at low dilutions in non-polar solvents where cohesive forces are of less account, might give some idea of the enolisation tendency of the tetronic acids.

The enolisation tendency is defined by the equation:

$$\Delta G_{KE} = -RT \text{ Ln.} K_{KE}$$

(where ΔG_{KE} is the free energy for the keto-enol change)

and for determination of the quantity, measurements of equilibrium in the gas phase are required, so that comparison of enolisation tendencies in substituted tetronic acids can only be made on a qualitative basis and similarly comparison with other enolic systems can only be made on such a basis.

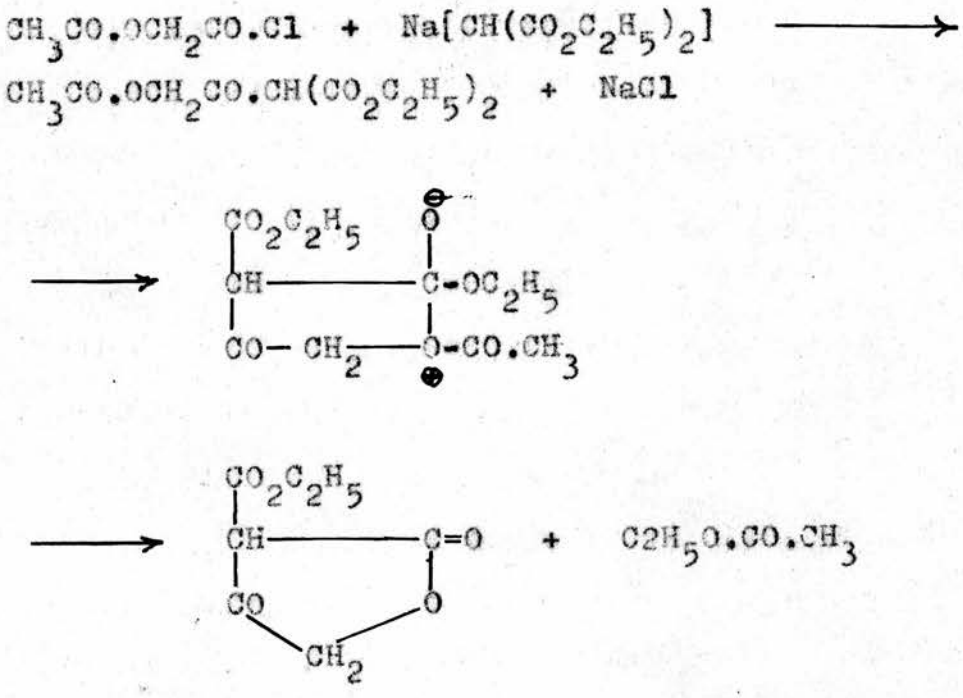
The tetronic acids therefore may, at present, be regarded as largely enolic and the solution of the problem of tautomeric equilibrium between ketonic and enolic forms requires measurements over a range of temperatures. The high melting points of these compounds renders impracticable measurement of equilibrium in the gas phase, so that more accurate observations on solutions of tetronic acids in non-polar solvents may increase our understanding of the problem.

PREPARATION OF TETRONIC ACIDS AND THEIR DERIVATIVES.

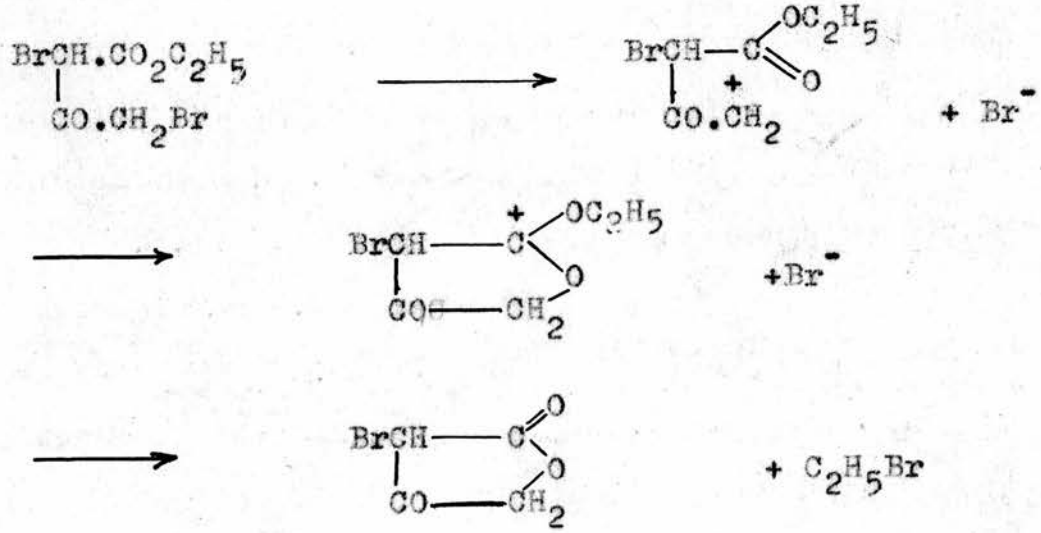
∝-Alkyl substituted tetronic acids were first prepared by E. Demarçay (Compt.rend.,1879,88,126) who obtained them by heating the corresponding ∝-alkyl-γ-bromoaceto-acetic ester when cyclisation to a tetronic acid occurs with loss of ethyl bromide. The acetoacetic ester was prepared by bromination of an ∝-alkylacetoacetic ester, followed by heating the resultant ∝-bromo compound in presence of hydrogen bromide when a migration of the bromine atom from the ∝ to the γ-position takes place. (A. Hantzsch, Ber.,1894,27,355,3168; M. S. Kharasch, E. Sternfeld and F. R. Mayo, J.Am.Chem.Soc.,1937,59,1655). ∝-Ethoxycarbonyl and ∝-methoxycarbonyl tetronic acids, from which tetronic acid may be obtained by saponification and subsequent decarboxylation, were prepared by R. Anschütz and W. Bertram by condensation of acetyl-glycollyl chloride with the appropriate sodio malonic ester (Ber.,1903,36,468; Ann.,1909,367,169; Ann.,1909. 368,23) and similarly E. Benary (Ber.,1907,40,1079) prepared ∝-carbethoxy tetronic acid by the action of chloracetyl chloride on sodio malonic ester.

H. Henecka suggested a mechanism for these reactions ("Chemie der Beta-Dicarbonyl Verbindungen", Springer Verlag, Berlin, 1950, p.183), which is shown in the scheme [1], for the cyclisation of the condensation product of

Scheme [I]



Scheme [II]



acetylglycollyl chloride with sodio malonic ester and in scheme [2] is shown the suggested mechanism for the cyclisation of $\alpha\gamma$-dibromoacetoacetic ester, which cyclises to α-bromotetronic acid on heating (L. Wolff and C. Schwabe, Ann.,1896,291,226).

Scheme [1] involves an addition of oxygen to the carbon atom of the carbethoxy group followed by separation of ethoxy and CH_3CO- groups as ethyl acetate. In scheme [2] a positive fragment, which arises by loss of a bromine ion from the intermediate compound, adds to the doubly bonded oxygen atom of the carbethoxy group. As there have been no studies concerning the mechanism of the reaction no critical discussion is possible. It is known, however, that it proceeds very readily under mild conditions and often in high yield and a selection of conditions is tabulated. The reaction seems to proceed very readily in polar solvents.

In the examples quoted ethyl acetate, ethyl benzoate and ethyl halides have all been eliminated from various β-keto esters. In every case the β-keto ester carried an α-substituent, whether electron releasing, such as an alkyl group, or electron attracting,such as a bromine atom or carbethoxy group. In the case of γ-bromoaceto-acetic ester, where no α-group is present, cyclisation does not occur on heating alone or with sodium ethoxide (Private communications from A. H. Stanners; F. Reuter

Table of Cyclisation Reactions.

Compound formed.	Cyclisation Conditions.	Reference.
∝-Methyl tetronic acid from $CH_2BrCO.CH(CH_3)CO_2Et$	heat 2 hours at 120°.	L. Wolff, Ann., 1895, 288, 1.
do.	heat in water.	R. Fittig, Ber., 1883, 16, 1939.
do. from $CH_3CO.CBr(CH_3)CO_2Et$	heat in presence of HBr.	P. C. Freer, Am.Chem.J., 1895, 17, 779.
∝∝-Dimethyl tetronic acid from $CH_3COOCH_2COCMe_2CO_2Et$	Standing alone for one month at room temp.	M. Conrad, R. Gast, Ber., 1898, 31, 2726.
	Standing in conc H_2SO_4 below 8° for 2 days.	E. B. Reid, et al., J.Org.Chem., 1950, 15, 572.
∝-Ethoxycarbonyl tetronic acid from acetyl chloride and sodio malonic ester.	Heat for short period in ether on water bath.	E. Benary, Ber., 1907, 40, 1080.

Table of Cyclisation Reactions. (contd.)

Compound formed.	Cyclisation Conditions.	Reference.
∝-Methoxycarbonyl tetronic acid from $Na[CH(CO_2Me)_2]$ and $CH_3CO.OCH_2COCl$	Heat 20 hours in ether on water bath.	R. Anschütz and W. Bertram, Ber., 1903, 36, 471.
do. with $CH_2Cl.COCl$	Standing in ether 24 hours at room temperature.	E. Benary, Ber., 1911, 44, 1759.
∝-Acetamido-tetronic acid from $CH_2Cl.COCl$ and $CH_3C(NH_2)=CH.CO_2Et$	Heat 1.5 hours in pyridine on water bath, then 4 hrs. at 120-130° on an oil bath.	W. Baker, K. D. Grice, and A. B. A. Jansen, J.Chem.Soc., 1943, 241.
∝-Acetamido-γ-Methyl tetronic acid from $CH_3CHBrCOCl$ and $CH_3C(NH_2)=CH.CO_2Et$	Allowing reaction products to attain room temp. from -50° over 2hrs. then kept at 0°.	T. L. Rebstock and H. M. Sell, J.Am. Chem.Soc., 1952, 74, 274.
∝-Bromotetronic acid from ∝-γ-dibromoaceto-acetic ester.	Heat on oil bath at 120-130° and 20-30mm. pressure for 2-3 hours.	L. Wolff and C. Schwabe, Ann., 1896, 291, 226.

Table of Cyclisation Reactions. (contd.)

Compound formed.	Cyclisation Conditions.	Reference.
∝-Ethoxycarbonyl-methyl tetronic acid from $CH_2BrCO.CH(CH_2CO_2Et).CO_2Et$	Heat 2 working days 95-100° at 20-30mm. pressure.	F. Reuter and R. B. Welch, J.Proc.Roy.Soc. N.S.W.,1939,72,120.
∝-Hydroxytetronic acid from Claisen condensation of ethyl benzoyl-glycollate.	Heat 3-4 hours in pyridine on water bath.	F. Micheel and F. Jung, Ber., 1933,66,1291.

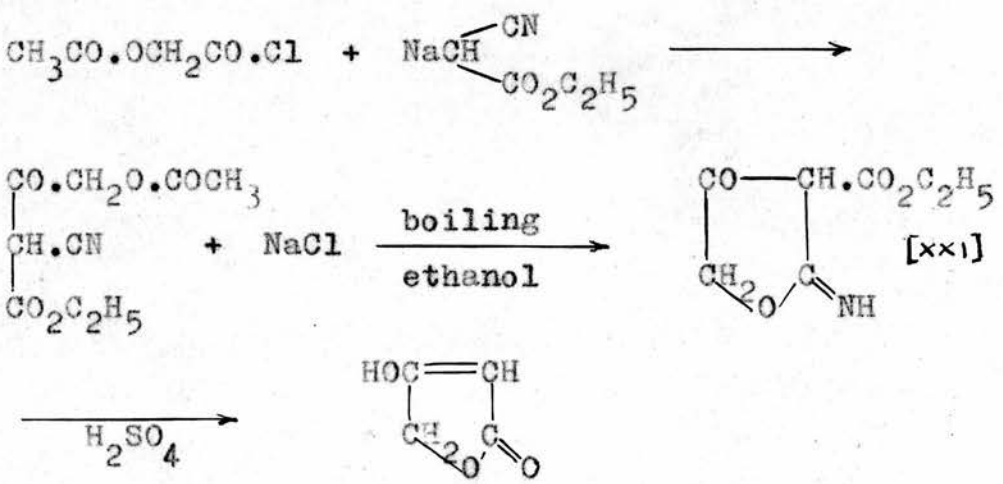
and R. B. Welch, J.Proc.Roy.Soc.N.S.W.,1939,72,120). However, a small quantity of tetronic acid was obtained by vacuum distillation of the product from the action of the magnesio derivative of the benzyl ester of bromo-acetic acid on methyl bromoacetate (A. C. Röttinger and F. Wenzel, Monatsh.,1914,34,1867).

The presence of an enolisable α-hydrogen atom does not appear to be necessary, as αα-dimethyl-γ-acetoxy-acetoacetic ester cyclises on standing for one month to αα-dimethyl-β-keto-γ-butyrolactone (M. Conrad and R. Gast., Ber.,1898,31,2726).

L. Wolff and C. Schwabe (loc.cit.), originally obtained tetronic acid by reduction of α-bromotetronic acid with sodium amalgam. The method has been improved by catalytic reduction (Pd on charcoal) in presence of baryta water which removes hydrogen bromide (F. Reuter and R. B. Welch, loc.cit., P. W. Clutterbuck, H. Raistrick and F. Reuter Biochem.J.1935,29,1300). The parent compound has also been prepared by action of strong sulphuric acid on the barium salt of tetronic acid α-carboxylic acid, the free acid is unstable and immediately decarboxylates on formation producing tetronic acid (F. Reuter and R. B. Welch, loc.cit.). Esters of α-carbethoxy tetronic acids may be saponified by treatment with alcoholic potassium hydroxide solution (E. Benary, Ber.,1907,40,1080) or by action of sodium

hydroxide in aqueous methanol (R. Anschütz and W. Bertram, Ber.,1903,36,471). This method has been used for preparation of many mono or di-substituted tetronic acids by decarbethoxylation of the corresponding ∝-carbethoxy tetronic acid obtained, as already outlined, by reaction of an acid chloride with sodio malonic ester followed by cyclisation (R. Anschütz and R. Böcker, Ann.,1909,368,53; E. Benary, Ber.,1911,44,1759; J. Lecocq, Compt.rend.,1946,222,299)

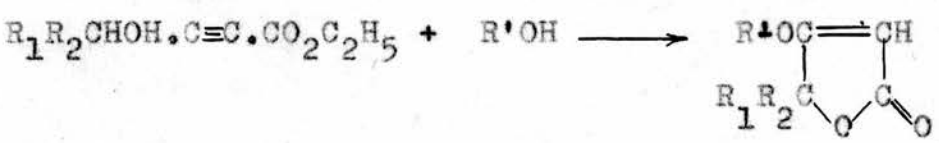
Tetronic acid has been obtained by action of sulphuric acid ∝-carbethoxy-imido-tetronic acid [XXI], which was prepared by action of boiling ethanol on the product resulting from condensation of acetylglycollyl chloride with the sodio derivative of cyanoacetic ester (R. Anschütz and W. Bertram, Ber.,1912,45,2374).



Tetronic acid may be regarded as the lactone of γ-hydroxy acetoacetic acid and the γ-ethoxy derivative of ethyl acetoacetate has been prepared by condensation

of ethyl acetate and ethyl ethoxyacetate under Claisen conditions (C. Weizmann, H. Stephen and G. S. Agashe, J.Chem.Soc.,1913,1855) and also by the action of ethyl bromoacetate and zinc amalgam on ethyl ethoxyacetate (T. B. Johnson and L. H. Chernoff,J.Am.Chem.Soc.,1914, 36,1742). However, γ-ethoxy acetoacetic ester is a typical β-keto ester, unlike the tetronic acids.

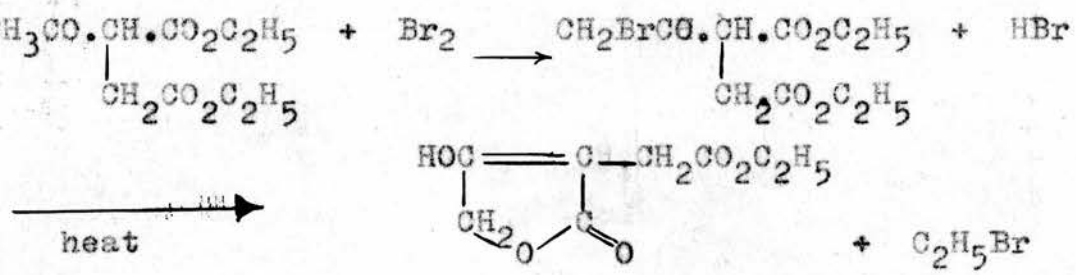
More recently γ-substituted tetronic acids have been synthesised from acetylenic intermediates by E. R. Jones and M. C. Whiting (J.Chem.Soc.,1949,1419). Addition of secondary amines to the triple bond of esters of γ-hydroxy-∝β-acetylenic acids gave β-substituted γ-lactone which could be hydrolysed by concentrated hydrochloric acid to the corresponding γ-mono or disubstituted tetronic acid. Similarly these authors found that addition of alcohols to the triple bond of esters of γ-hydroxy-∝β-acetylenic acids (catalysed by alkali alkoxide or BF_3/HgO) occurred with the formation of the corresponding ether of a substituted tetronic acid.



The method has been employed by R. A. Raphael to prepare the lactone 3-hydroxy-2-methoxy-4-methylpenta-1:4-diene-carboxylic acid (J.Chem.Soc.,1947,805) and also

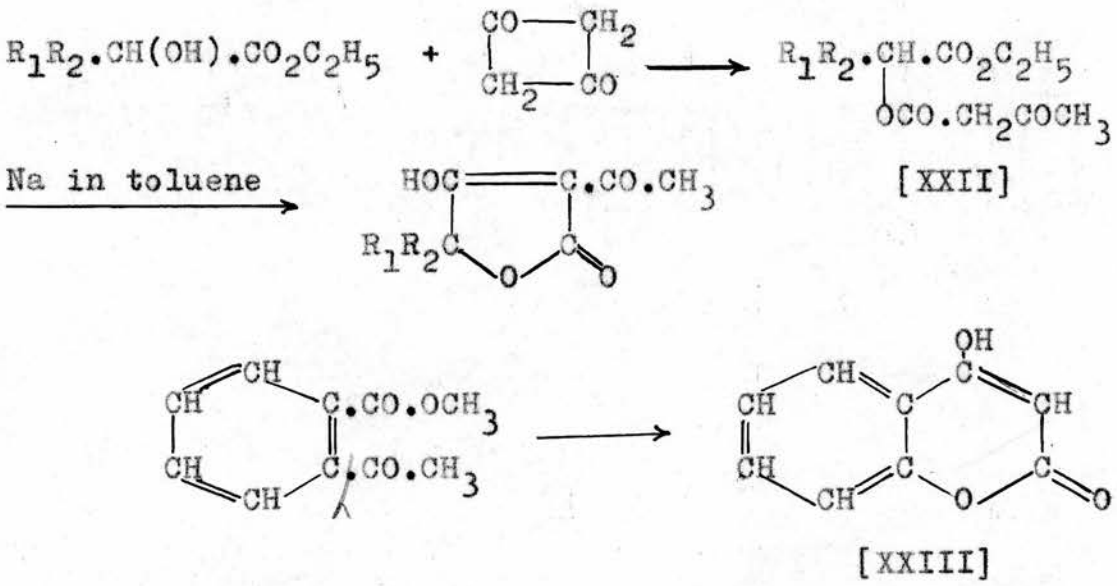
to synthesise penicillic acid (J.Chem.Soc.,1948,1508).

∝-Ethoxycarbonyl tetronic acid was prepared by bromination of diethyl acetylsuccinate, cyclisation of the product being then effected by heating under diminished pressure (S. Ruhemann and A. S. Hemmy, J.Chem.Soc.,1897, 329; F. Reuter and R. B. Welch, loc.cit.)



A more recent synthesis giving excellent yields has been described by R. N. Lacey (J.Chem.Soc.,1954,832). By reaction of keten dimer with a hydroxy acid, an ester of acetoacetic acid [XXII] is formed and this when treated with sodium in boiling xylene undergoes a Dieckmann type of cyclisation to give an acetyl tetronic acid. This method of internal cyclisation was first used by H. Pauly and K. Lockemann (Ber.,1915,48,28) for the synthesis of 4-hydroxycoumarin [XXIII] from acetyl methyl salicylate which cyclised on heating in presence of sodium and the method has now been extended to simple tetronic acids (A. H. Stanners: private communication). From ethyl phenylacetyl lactate, γ-methyl-∝-phenyl

tetronic acid could be obtained in 60% yield when diisopropylamine ~~ethyl~~ magnesium bromide was used as the condensing agent.



[XXII]

[XXIII]

Attempts to utilise a synthesis involving an organometallic derivative of tetronic acid as a route to ∝-substituted tetronic acids have met with no success (F. Reuter and R. B. Welch, loc.cit.) although what is probably ∝-carbethoxy-∝-acetyl tetronic acid has been obtained by the action of acetyl chloride on the compound prepared by the action of sodium wire on ∝-carbethoxy tetronic acid in dioxan.

REACTIONS OF TETRONIC ACIDS.

Tetronic acid is strongly acidic and forms stable salts (W. D. Kumler, J.Am.Chem.Soc.,1938,60,859). It gives a red coloration with ferric chloride solution, typical of an enolic system. It is extremely stable and no degradation or opening of the ring occurs on boiling with sodium hydroxide solution. As a ketone it reacts with phenylhydrazine to give a phenylhydrazone m.p.128° (L. Wolff and C. Schwabe Ann.,1896,291,226). It also gives an oxime m.p.144° (idem.ibid.).

Many reactions of tetronic acid which involve attack at the α-position are analogous to those of which occur at the ortho position of a phenol. The α-position is a centre of attack for electrophilic reagents and nitration, sulphonation and bromination readily give the corresponding α-substituted tetronic acid. Benzene diazonium chloride couples in the α-position to give the α-phenylhydrazone of αβ-diketobutyrolactone for which several formulae may be written as [I]-[III]. As with phenolic compounds O-acetyl, O-benzoyl and O-alkyl derivatives may be prepared by conventional methods. The ethers of tetronic acid are very resistant to alkaline hydrolysis (R. Moscheles and H. Cornelius, Ber.,1888,21, 2603; E. R. H. Jones and M. C. Whiting, J.Chem.Soc., 1949,1423).

Tetronic acids which are unsubstituted in the ∝-position give a purple colour with sodium nitrite solution. ∝-Oximido-tetronic acid [VI] (L. Wolff and C. Schwabe, loc.cit.) is formed, which gives purple coloured salts with alkali metals.

Two molecules of tetronic acid condense at room temperature with one molecule of a carbonyl compound to give alkylidene bis-tetronic acids (L. Wolff and W. Schlimpff, Ann.,1901,315,151) e.g. with acetone, isopropylidene-bis-tetronic acid, [V] is formed.

When a concentrated aqueous solution of tetronic acid is heated and left to stand, anhydrotetronic acid m.p.263° (d.) (L. Wolff and C. Schwabe loc.cit.) separates. It may also be prepared by heating tetronic acid in N-methyl morpholine (D. H. Marrian, P. B. Russell and A. R. Todd, J.Chem.Soc., 1947,1365) and its constitution has been shown to be [IV], arising by condensation of two molecules of tetronic acid with elimination of water (D. H. Marrian, P. B. Russell and A. R. Todd, loc.cit.). In spite of this formulation, no γ-substituted tetronic acids would condense in the same manner to give anhydro compounds as might be expected.

The chromic acid oxidation of tetronic acids has been studied by E. B. Reid, R. B. Fortenbaugh and H. R. Paterson (J.Org.Chem.,1950,15,572) who found that ∝-diketones were produced before hydrolysis of the lactone ring occurred,

subject to 3 conditions:-

1) Enolisation must be possible, i.e. the ∝-position must not be disubstituted.

2) If the ∝-position is unsubstituted then the γ-position must bear only one substituent.

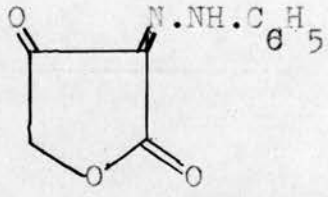
3) If the ∝-position is monosubstituted then a diketone is produced regardless of substituents at the γ-position.

In a recent paper, W. Cocker and co-workers (J.Chem.Soc., 1955,588) have discussed the iodoform reaction and found that a positive reaction is given by ∝-methyl tetronic acid and ∝-γ-dimethyl tetronic acid.

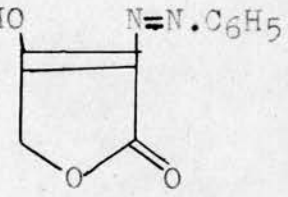
Derivatives of tetronic acid.

The γ-alkyl derivatives of tetronic acid show the same chemical behaviour as the parent compound. Similar behaviour is shown by the ∝-alkyl derivatives but reactions which involve replacement of a hydrogen atom at the ∝-position (e.g. bromination) give non-acidic compounds as enolisation can no longer occur.

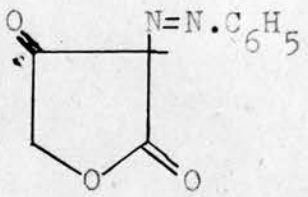
Acetyl tetronic acid possesses a triketo system and is strongly acidic (W. Baker, K. D. Grice and A. B. A. Jansen, J.Chem.Soc.,1943,241). The reactivity of the $-CH_3$ group in the $-CO.CH_3$ group is diminished and condensation with an aldehyde gives only a poor yield of the corresponding unsaturated derivative [VII] (W. Baker, K. D. Grice and A. B. A. Jansen, loc.cit.) but the usual derivatives of



[I]



[II]



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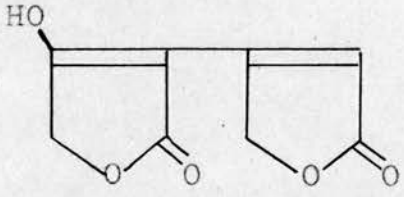
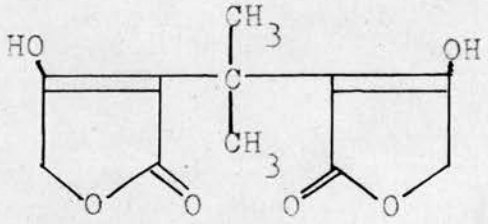
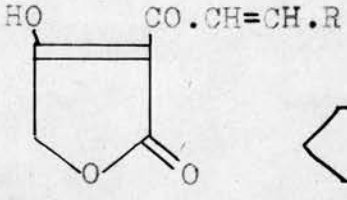


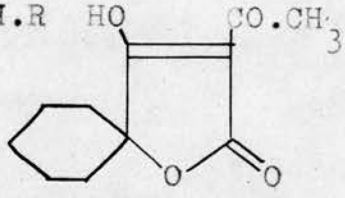
[IV]



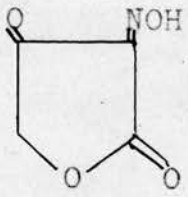
[V]



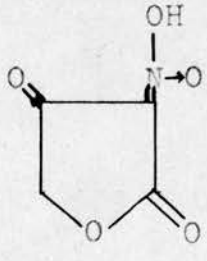
[VII]



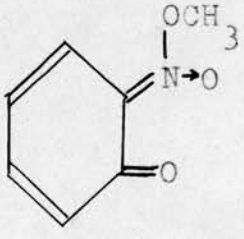
[VIII]



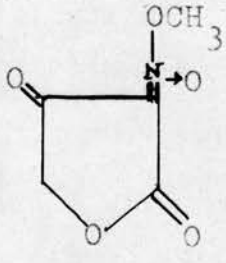
[VI]



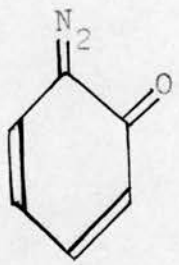
[IX]



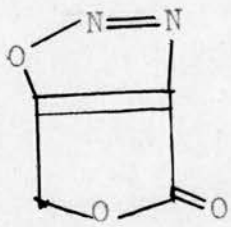
[XI]



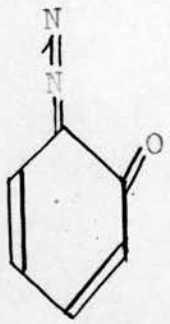
[X]



[XIII]



[XII]



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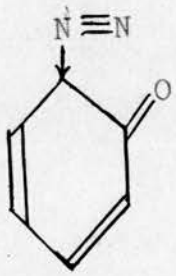
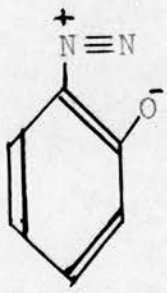
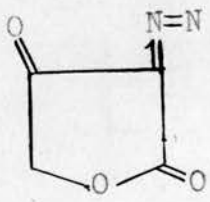


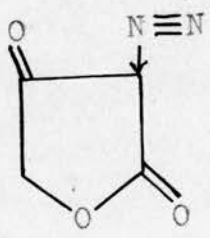
[XV]



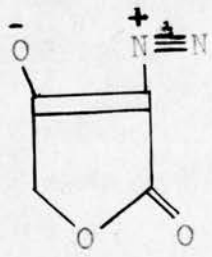
[XVI]



[XVII]



[XVIII]



[XIX]

$R.CO.CN_2.COOC_2H_5$

[XX]

the acetyl carbonyl group can be prepared without difficulty. Reduction of the compound with palladium on charcoal gives ∝-ethyl tetronic acid (P. W. Clutterbuck H. Raistrick and F. Reuter, Biochem.J.1935,29,300). Dehydracetic acid can similarly be reduced to 3-ethyl-6-methyl-pyronone (J. A. Berson, J.Am.Chem.Soc.,1952,74,5172). Like tetronic acid, ∝-acetyl tetronic acids are unaffected by boiling in sodium hydroxide solution and the compound [VIII] is stable in boiling concentrated hydrochloric acid or in 80% sulphuric acid at 100°. (R. N. Lacey, J.Chem.Soc.,1954,832).

∝-Nitrotetronic acid is prepared by nitration of tetronic acid at -5° or by oxidation of ∝-oximido-tetronic acid (L. Wolff and A. Luttringhaus, Ann.,1900,312,119). It has pK_a 1.68 and, on the basis of its dipole moment, appears to be enolic (W. D. Kumler, J.Am.Chem.Soc., 1942,64,1948) but gives no colour with ferric chloride solution. This behaviour is parallelled by that of o-nitrophenol which gives no colour with ferric chloride. ∝-Nitrotetronic acid forms a methyl ester from which an oxime can be prepared and on this evidence the ether [X] was formulated by L. Wolff and A. Luttringhaus (loc.cit.) as derived from a pseudo-acid [IX]. (cf. [XI] which can be obtained from o-nitrophenol (N. V. Sidgwick, "Organic Chemistry of Nitrogen", Oxford University Press, Oxford, 1942, p.267).

∝-Aminotetronic acid is obtainable as colourless needles, which decompose at 250°, by reduction of ∝-nitrotetronic acid with tin or zinc in acid or with sodium amalgam (L. Wolff and A. Luttringhaus, loc.cit.).

∝-Amino-γ-methyl tetronic acid has been prepared by reduction of the diazo compound obtained by action of benzene diazonium chloride on γ-methyl tetronic acid (J. Lecocq., Bull.Soc.chim.,1951,18,183; cf. F. Micheel and R. Mittag, Z.Physiol.Chem.,1937,247,34). Like the amino-phenols, aminotetronic acids are very easily oxidised.

With nitrous acid a "diazo anhydride", formulated as [XII] by L. Wolff and A. Luttringhaus (loc.cit.), is formed. This, however, they consider does not behave as a true diazo compound except in acid solution when the ring is cleaved to give a compound of true diazo character. In alkaline solution it couples with ∝-naphthol to give a brown dye. Later Wolff suggests that the compound resembles diazotised ortho-aminophenol which he wrote as [XIII]. This compound is discussed by N. V. Sidgwick ("Organic Chemistry of Nitrogen" Oxford University Press, Oxford, 1942,p.422 and p.360) and the diazo-phenol is probably a resonance hybrid of structures [XIV]-[XVI]. A similar formulation [XVII]-[XIX] seems very probable in the case of diazo tetronic acid and would account for the properties of the compound as well as the anhydro ring form. This compound also has a parallel in the very

stable aliphatic diazo compounds or "diazo anhydrides" [XX] obtained by action of acyl chlorides on diazoacetic ester (L. Wolff, Ann.,1903,325,129) and in such compounds the adjacent carbonyl groups exert a considerable stabilising effect on the diazo group and reduce its reactivity.

α-Hydroxytetronic acid (F. Micheel and F. Jung, Ber., 1933,66,1291; 67,1660) is prepared by a Claisen condensation of ethyl benzoyloxyacetate. In an impure state it may be obtained by hydrolysis of α-bromotetronic acid (L. Wolff and C. Schwabe, loc.cit.). Recrystallised from ether it has m.p.153° and it is very easily oxidised, especially by iodine or in presence of a trace of cupric ion, to αβ-diketo-γ-butyrolactone.

α-Ethoxycarbonyl tetronic acid is obtained by condensation of chloroacetyl chloride with the sodio derivative of malonic ester (E. Benary, Ber.,1907,40,1080). Recrystallised from methanol it has m.p.124-125°. It may be regarded as the ester of the unknown tetronic acid α-carboxylic acid. Salts of this acid obtained by alkaline hydrolysis of the ester lose carbon dioxide immediately on acidification to give the parent tetronic acid.

α-Methoxycarbonyl tetronic acid m.p.188-9°(d.) (E. Benary, Ber.,1911,44,1759) was prepared in the same fashion by the action of acetylglycollyl chloride on the sodio derivative of dimethyl malonate (R. Anschütz and

W. Bertram, Ber.,1903,36,471).

∝-Bromotetronic acid (L. Wolff and C. Schwabe, loc.cit.) is prepared by bromination of tetronic acid in chloroform in the absence of water. If water is present the unstable ∝∝-dibromotetronic acid is formed. ∝-Bromotetronic acid crystallises from water as needles or prisms m.p.183°(d.). It gives a violet colour with sodium nitrite solution as the bromine atom is readily displaced by this reagent. On sodium amalgam reduction or on catalytic reduction (P. W. Clutterbuck, H. Raistrick and F. Reuter.,Biochem. J.1935,29,1300).the bromine atom is replaced by hydrogen. The bromine atom is relatively unreactive towards attack by aqueous alkali or ethanolic potassium acetate.

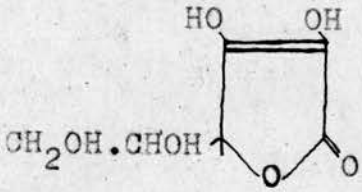
∝-Iodotetronic acid (L. Wolff and A. Luttringhaus, loc.cit.) is obtained by the action of iodine on a cold solution of tetronic acid. The compound decomposes with evolution of gas at 178-180°.

Tetronic acid ∝-sulphonic acid (L. Wolff and A. Luttringhaus, loc.cit.) prepared by the action of fuming sulphuric acid on tetronic acid is said to be neutral. It crystallises from ethanol/ether as needles m.p.83°.

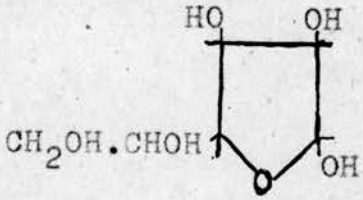
NATURALLY OCCURRING TETRONIC ACID DERIVATIVES.

The tetronic acid system, like many other unsaturated lactone systems, occurs in natural products. The most important naturally occurring derivative is ascorbic acid [I] (Vitamin C) the chemistry and physiological activity of which has been reviewed adequately elsewhere (T. Reichstein and V. Demole, "Festschrift für E. C. Barell", Basel 1936, p.107; E. L. Hirst, "Fortschritte der Chemie Organischer Naturstoffe", Vienna 1939,p.132; F. Smith, "Advances in Carbohydrate Chemistry", Vol II, Academic Press, New York,1946,p.79). This compound has been discussed mainly from the standpoint of monosaccharide chemistry but it may be regarded as derived from α-hydroxy-tetronic acid. However, the latter does not possess the antiscorbutic activity of vitamin C in spite of the similarity of its chemical behaviour, notably the easily oxidisable ene-diol system. Whilst ascorbic acid is of wide occurrence the other tetronic acid derivatives known have been isolated as mould metabolic products or as pigments from lichens.

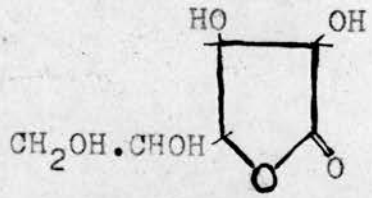
The biochemistry of moulds has been reviewed by P. W. Clutterbuck (J.Soc.Chem.Ind.1936,55T) in an article in which he makes special reference to the work of H. Raistrick and co-workers, who approached the problem



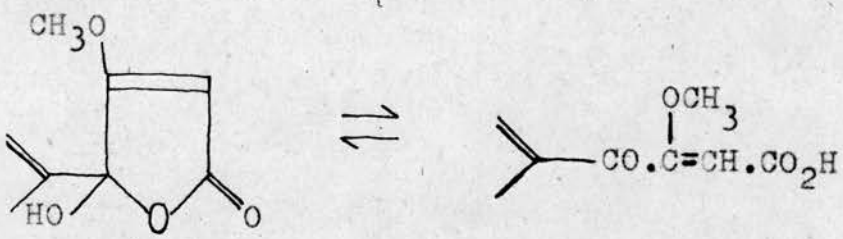
[I]



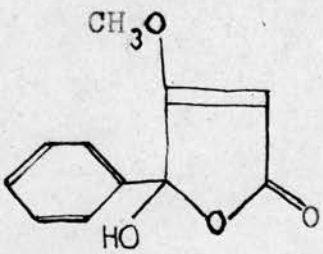
[II]



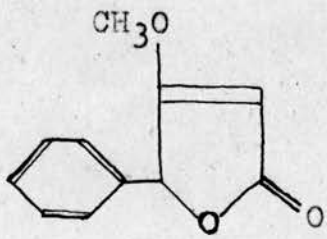
[III]



[IV]



[V]



[VI]

systematically by selecting 400 representative pure cultures of moulds and examining the metabolic products. Many types of organic compound were isolated:- organic acids, later recognised as intermediates in the tricarboxylic acid cycle; phenols and condensed hydroxylated aromatic systems and many more compounds such as penicillic acid, penicillin, puberulic acid, ascorbic acid and tetronic acids.

Tetronic acid derivatives were obtained from Penicillium Charlesii and the reviewer suggested that their occurrence should be considered in relationship to the polysaccharide elaborated by this organism. A polygalactose of nine or ten galactofuranose units mutually linked through the 1,5 positions was isolated. Bromine oxidation of methylated galactofuranose gave a compound [III] which approaches the tetronic acid system and Clutterbuck proposed that such a polysaccharide may be an intermediate in the formation of characteristic metabolites. The isolation of characteristic products even when there are variations in the substrate of the mould would be explained by the hypothesis that the synthesis of a particular polysaccharide is an intermediate stage in metabolism.

H. Raistrick in the Bakerian lecture for 1950 (Proc.Roy.Soc.,1950,199A,141) has given a summary of many of the more important structural types of mould

metabolites which have been isolated. Many of these mould metabolites show antibacterial activity. However, tetronic acid derivatives from P. Charlesii did not possess such activity although L. J. Haynes (Quart. Reviews,1948,2,50) has suggested that it is possible that concentrations of the order of 1 in 1000 were not tested.

Penicillic acid [IV] is a tetronic acid derivative, which was first isolated from culture filtrates of Penicillium puberulum (C. L. Alsberg and O. F. Black, U.S.Dep.Agric.Bur.Plant Ind.Bull.,1913,No.270) and has since been isolated from the metabolic products of P. cyclopium, (J. H. Birkinshaw, A. E. Oxford and H. Raistrick, Biochem.J.1935,30,394) Aspergillus ochraceus, P. Thomii, P. suavolens, (E. O. Karow, H. B. Woodruff and J. W. Foster, Arch.Biochem.,1944,5,279) and P. aurantiovirens (A. R. Todd and C. Hassall, quoted by L. J. Haynes, Quart.Reviews,1948,2,52).

Penicillic acid whilst possessing the same toxicity as phenol, completely suppresses the growth of Staphylococcus aureus at a concentration of 1 in 50,000, whereas phenol only partly suppresses the growth of this organism at a concentration of 1 in 1000 (A. E. Oxford, H. Raistrick and G. Smith, Chem.and Ind.,1942,61,22; A. E. Oxford, ibid.,p.48). Penicillic acid is much more active than penicillin against Gram-negative bacteria but is not so

effective against Gram-positive.

It has been synthesised by means of acetylenic intermediates by R. A. Raphael (J.Chem.Soc.,1948,1508) who has also synthesised analogous compounds such as [V] (J.Chem.Soc.,1948,118).

The compound [V] showed only one quarter of the antibacterial activity of penicillic acid itself, but it is of interest that the methyl ether of γ-phenyl tetronic acid [VI] which was also synthesised and tested was found to be 30 times as active as the natural antibiotic.

Tetronic acid derivatives from Penicillium Charlesii.

The mould Penicillium Charlesii G. Smith, obtained from mouldy Italian maize, when grown on a nutrient medium containing glucose, produced 2 polysaccharides, mannocarolose (W. N. Haworth, H. Raistrick and M. Stacey, Biochem.J.1935,29,612) and galactocarolose, together with some new organic acids (P. W. Clutterbuck, W. N. Haworth, H. Raistrick, G. Smith and M. Stacey, Biochem.J.1934,28,94).

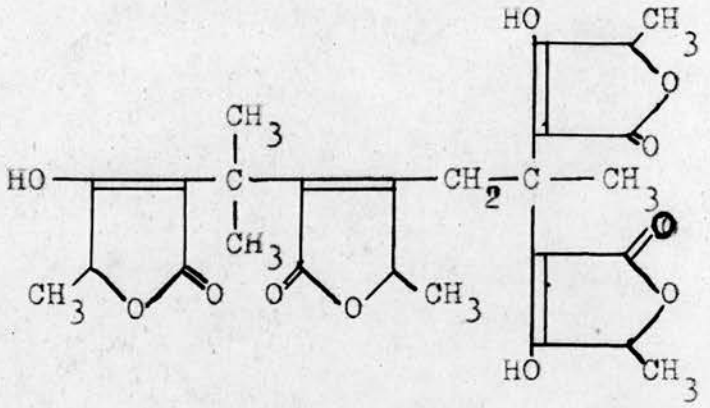
Carolic acid and carolinic acids were isolated in greatest yield, lower yields of carlic acid and carlosic acid were also obtained. Two other acids, ramigenic acid and verticillic acid, were also isolated in small quantity but it was shown that they were artefacts formed by a condensation of methyl tetronic acid with the acetone which was used in the isolation procedure (P. W. Clutterbuck,

H. Raistrick and F. Reuter, Biochem.J.,1935,29,1300). The condensation was found to take place even in dilute aqueous solution at ordinary temperatures and especially in presence of dilute hydrochloric acid to give isopropylidene-bis-γ-methyl tetronic acid which further condenses with a second molecule of acetone to produce acetonyl isopropylidene-bis-γ-methyl tetronic acid [VIII] and this was found to be identical with ramigenic acid. Verticillic acid when hydrolysed by standing with dilute hydrochloric acid, gave 1 molecule of ramigenic acid and 2 molecules of γ-methyl tetronic acid and was therefore formulated as [IX].

This was confirmed by replacing acetone by ethanol to precipitate carbohydrates when l-γ-methyl tetronic acid was isolated in yields of the same order as would be expected for ramigenic and verticillic acids and is therefore regarded as a true metabolic product.

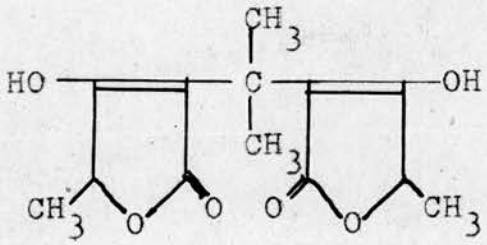
The constitution of the four metabolic acids was elucidated by degradative methods (P. W. Clutterbuck, H. Raistrick and F. Reuter, Biochem.J.,1935,29,300; 1935,29,871) and their relationship to α-acetyl tetronic acid was shown by a study of their absorption spectra (R. W. Herbert and E. L. Hirst, Biochem.J.,1935,29,1881)

The structures indicated were assigned to carolic acid [X], m.p.132°, $[\alpha]_{5461}$ +84°; carolinic acid [XI], m.p.123° (d.), $[\alpha]_{5461}$ +60°; carlic acid [XII], m.p.176°,



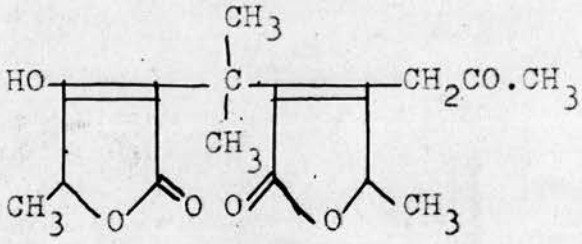
[IX]

Verticillic acid.



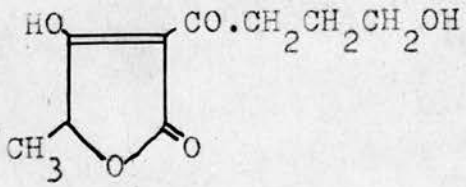
[VII]

Isopropylidene-bis-γ-methyl tetronic acid.



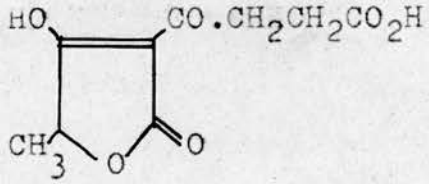
[VIII]

Ramigenic acid.



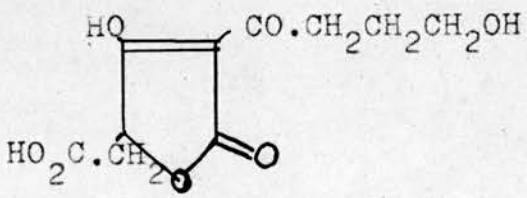
[X]

Hydrated carolic acid.



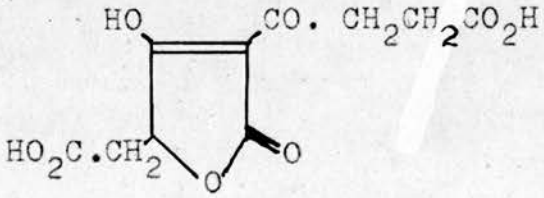
[XI]

Carolinic acid.



[XII]

Hydrated carlic acid.



[XIII]

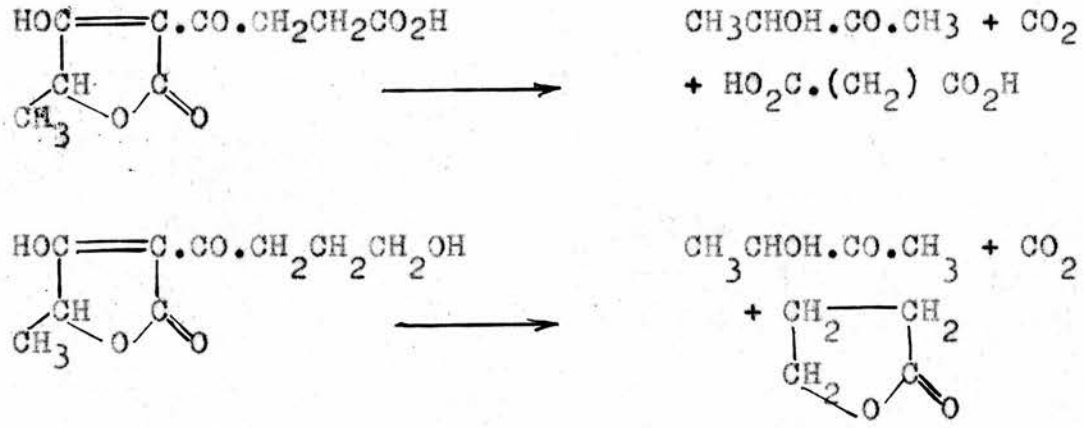
Carlosic acid.

$[\alpha]_{5461}$ -160°; carlosic acid [XIII] m.p.181°, $[\alpha]_{5461}$ -160°. The methyl tetronic acid was present as l-γ-methyl tetronic acid m.p.117°, $[\alpha]_{5461}$ -21°.

All the acids gave orange ferric chloride colours. Their reaction with 2:4-dinitrophenylhydrazine was slow. On bromination carolinic acid and carolic acid gave α-bromo—l-γ-methyl tetronic acid, but gave no colour with sodium nitrite indicating that if the tetronic acid nucleus was present the α-position carried a substituent.

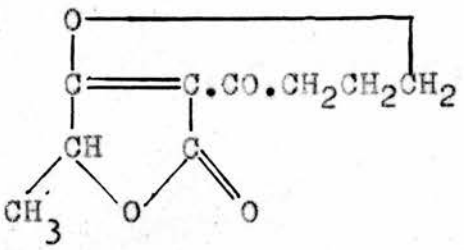
On reduction in the presence of palladium on charcoal carolinic and carlic acids took up 2 molecules of hydrogen to give compounds and these from their properties and from the similarity of their absorption spectra to that of α-ethyl tetronic acid (R. W. Herbert and E. L. Hirst, loc.cit.), which was similarly produced by reduction of α-acetyl tetronic acid, were ascribed the formula of tetronic acid derivatives carrying a saturated side chain.

Hydrolysis of the two acids with 2N sulphuric acid gave an indication of the nature of the side chain. Carolic acid gave carbon dioxide (1 mol.) acetoin (1 mol.) and hydroxy butyric acid (as butyrolactone) carolinic acid gave carbon dioxide (1 mol.), acetoin (1 mol.) and succinic acid (1 mol.). The presence of acetoin and carbon dioxide suggests that these products may arise from a methyl tetronic acid fragment and the other products derive from the side chain of the molecule.

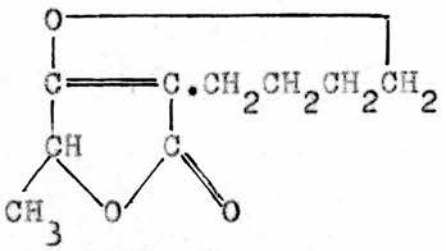


Carolinic acid is dibasic and possesses the expected properties. Carolic acid is monobasic but crystallises from ethanol with one molecule of water less than would be expected from the above formula and possesses no active hydrogen atoms (Zerewitinoff). In the section on the ultra-violet light absorption properties of tetronic acids the behaviour of carolic and carlic acids has been described and, unlike the other metabolic acids, which behave in the same fashion in aqueous and ethanolic solution, these two acids in aqueous solution show doubly banded spectra typical of the series but in ethanol show only a single absorption band (R. W. Herbert and E. L. Hirst, loc.cit.).

The loss of a molecule of water by carolic acid is parallelled in the behaviour of the reduction product, which readily loses water to give a neutral product to which formula [XV] has been ascribed.



[XIV]



[XV]

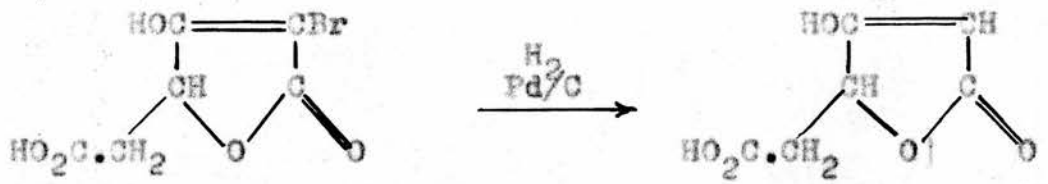
Anhydrous carolic acid.

Crystalline carolic acid has been formulated therefore as [XIV] (P. W. Clutterbuck, H. Raistrick and F. Reuter, Biochem.J.,1935,29,300).

In a similar manner the constitution of carlic and carlosic acids has been elucidated (idem.ibid.,1935,29, 871). Both acids are dibasic in water and on bromination both give a compound $C_6H_5O_5Br$ m.p.194°, probably 1-∝-bromo-γ-carboxymethyl tetronic acid [XVI] which on hydrogenation in the presence of palladium on charcoal gives 1-γ-carboxymethyl tetronic acid [XVII].

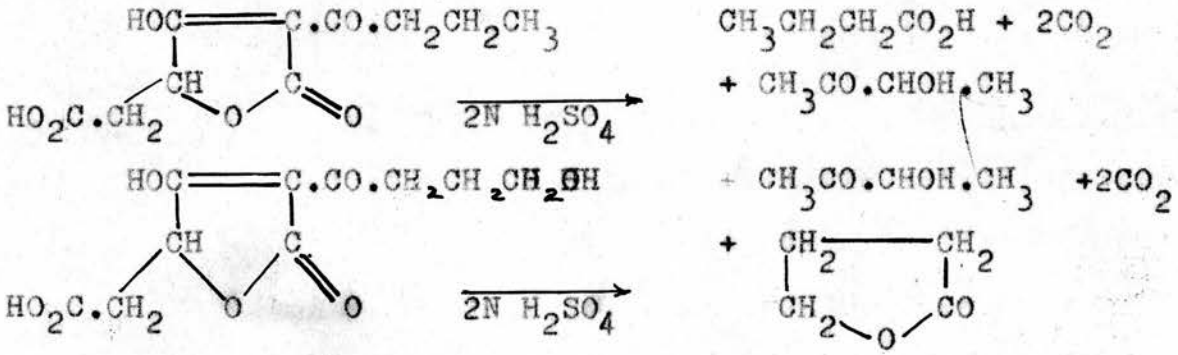
On hydrolysis with boiling 2N sulphuric acid, carlic acid gives acetoin (1 mol.), carbon dioxide (2 mols.) and butyrolactone (1 mol.) carlosic acid gives acetoin (1 mol.) carbon dioxide (2 mols.) and n-butyric acid (1 mol.). The first molecule of carbon dioxide is given off readily and the second only very slowly and this behaviour is parallelled in γ-carboxymethyl tetronic acid which loses the first molecule of carbon dioxide readily on treatment with 2N sulphuric acid, whereas the second is evolved

more slowly with the formation of acetoin.

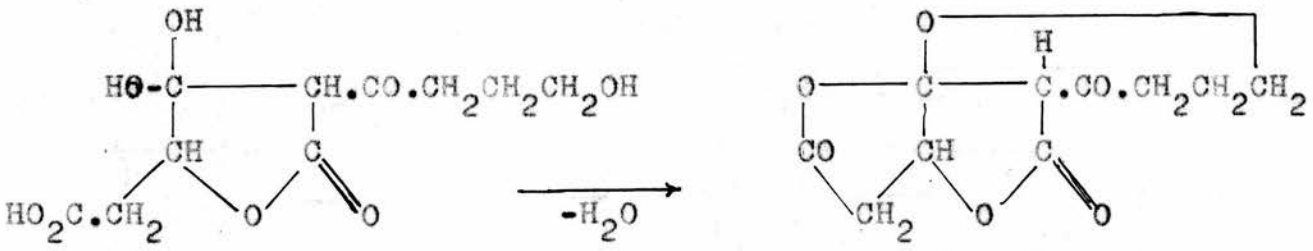


[XVI] [XVII]

Reduction of the acids required two molecules of hydrogen and the compounds obtained were formed by reduction of a side chain keto to a methylene group, light absorption thus altering from the ∝-acetyl tetronic acid type to the ∝-ethyl tetronic acid type.



In view of the fact that carlic acid has no active hydrogen atoms (Zerewitinoff) and in the crystalline state it possesses a formula $C_{10}H_{10}O_6$ the formula [XVIII] was put forward, and this structure is derived from a hydration of a tetronic acid keto group followed by loss of water.

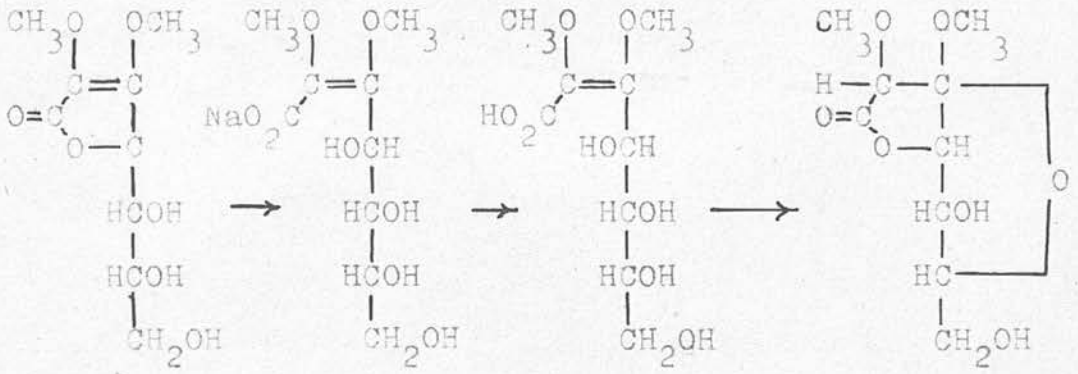


[XVIII]

The relation between carlic acid and carolic acid on the one hand and carolinic acid and carlosic acid on the other is noteworthy and any structural formulae which may be put forward must indicate this relationship and explain the different light absorption behaviour of the two groups in aqueous and ethanolic solution.

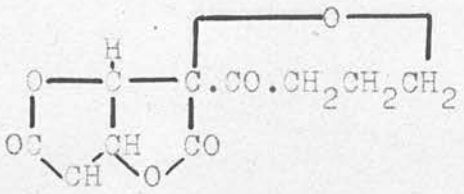
A possible modification of the formula [XVIII] put forward for carlic acid has been suggested (W. N. Haworth, E. L. Hirst, and J. K. N. Jones, J.Chem.Soc., 1937, 549) in the light of work on analogues of ascorbic acid where simultaneous lactonisation and ring formation by saturation of a double bond were found to occur. When 2:3-dimethyl gluco-ascorbic acid [XIX] was treated with alkali and the product was acidified an acid [XX] was formed which lactonised forming isodimethyl gluco-ascorbic acid [XXI] when attempts were made to isolate it.

These authors considered that by a similar type of isomerisation hydrated carlic acid may give rise to carlic acid and therefore a structure such as [XXII] appeared equally as probable as that of P. W. Clutterbuck,

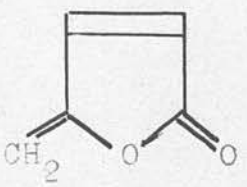


[XIX] [XX] [XXI]

Isodimethyl gluco-ascorbic acid.

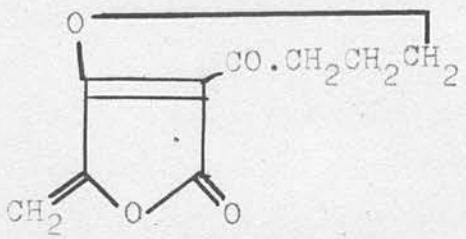


[XXII]

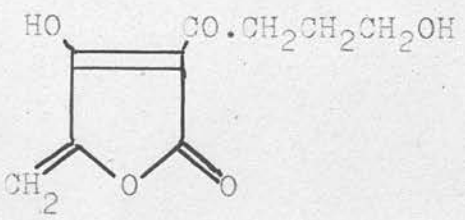


[XXV]

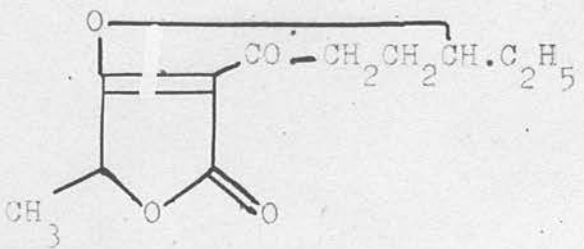
Protoanemonin



[XXIII]



[XXIV]



[XXVI] Terrestric acid.

H. Raistrick and F. Reuter (loc.cit.) which contains a seven membered ring.

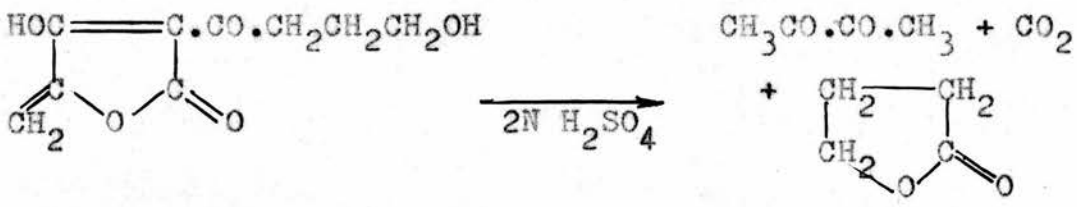
Although structure [XXII] seems more probable on steric grounds, it is difficult to reconcile the appearance of the absorption band at 2700A.($\varepsilon_{max.}$ 16,500) (R. W. Herbert and E. L. Hirst, loc.cit.), which is observed in an ethanolic solution of carlic acid, with a formula such as [XXII] which contains only isolated carbonyl groups and so would be expected to show only very slight absorption. The direction of addition to the double bond to give structure [XVIII] is analogous to that which gives structure [XXI] i.e. the oxygen atom adds to the β-carbon atom and the hydrogen atom to the α-carbon atom, whereas in the formation of [XXII] this mechanism is reversed and this seems less likely on electronic grounds.

From Penicillium cinerascens Biourge grown on a glucose containing medium H. Raistrick and A. Bracken (Biochem.J.1947, 41,569) isolated dehydrocarolic acid which possessed structure [XXIII] or in the hydrated form [XXIV]. Small amounts of carlosic acid were also isolated.

Dehydrocarolic acid has no definite melting point but tends to polymerise on heating above 80° alone or in many, especially polar, solvents. (In this respect it resembles protoanemonin [XXV] which polymerises at room temperature). It is monobasic and gives an orange colour with ferric chloride solution.

With ozone, formaldehyde is obtained indicating the presence of a $CH_2=C<$ group. Reduction in presence of palladium on charcoal produces dl-carolic acid. Like carolic acid, it is readily soluble in chloroform but, unlike this acid which in aqueous solution is dextrorotatory, dehydrocarolic acid is optically inactive.

When the acid is hydrolysed with 2N sulphuric acid, some polymerisation occurrs and diacetyl, carbon dioxide and butyrolactone are produced but not quantitatively.



From this evidence its structure has been formulated by H. Raistrick and A. Bracken (loc.cit.) as [XXIII].

Terrestric acid(ethyl carolic acid) [XXVI] (J. H. Birkinshaw and H. Raistrick,,Biochem.J.,1936,30,2194) is a metabolic product of Penicillium terrestre Jensen. Its similarity to the acids from P. Charlesii was shown by an orange colour with ferric chloride and by the production of d-α-bromo-γ-methyl tetronic acid on bromination.

It has m.p.89° and titrates as a monobasic acid in water but in pyridine it is found to contain no active hydrogen atoms. Hydrolysis with 2N sulphuric acid

produces carbon dioxide (1 mol.), acetoin (1 mol.) and a lactone, (1 mol.) which is optically active, identified as δ-hexanolactone.

These reactions show that terrestric acid bears a close relationship to carolic acid [X] and can be regarded as ethyl carolic acid, the ethyl group replacing a hydrogen atom of carolic acid in such a manner that another centre of asymmetry is created in the molecule.

The compound vulpinic acid [XXVII] occurs in Lichens such as Letharia vulpina, Cetraria tubulosa, in Cypheliaceae, Parmeliaceae, Usneaceae etc. as a pigment. (Mayer and Cook, "The Chemistry of Natural Coloring Matters", Reinhold, New York, p.156, 1943). It forms yellow leaflets m.p.148° and is the methyl ester of pulvinic acid [XXVIII] which has been synthesised (J. Volhard, Ann., 1894, 282, 1; M. Asano and Y. Kameda, Ber., 1935, 68, 1565).

Pinastrinic acid [XXIX] or [XXX] (Mayer and Cook, loc.cit.p.156), a yellow compound m.p.203-4°, occurs in Cetraria pinastris and Cetraria juniperina. It differs only from vulpinic acid by a methoxyl group.

Calycin (Mayer and Cook, ibid., p.157) from the Calyciaceae and Lepraria species forms orange red needles m.p.244-5°, and has the structure [XXXI].

Vulpinic acid possesses insecticidal properties.

In an examination of the factor responsible for the hatching of cysts of the potato eelworm (Heterodora

rostochiensis Wollenberger) A. R. Todd and co-workers did not succeed in isolating the factor but showed that anhydrotetronic acid was the only one of a large number of chemical types examined which possessed appreciable activity (C. T. Calam, A. R. Todd and W. S. Waring, Biochem.J.,1949,45,520). In the course of the research the structure of anhydrotetronic acid was established as [XXXII]. (D. H. Marrian, P. B. Russell, A. R. Todd and W. S. Waring, J.Chem.Soc.,1947,1365).

The varied occurrence of the tetronic acid system in nature has been outlined together with some account of its physiological activity. The varying physiological activities shown by tetronic acid derivatives show that further studies are desirable to extend knowledge of their value in this field. For example, the growth inhibiting or 'blastocholine' effect of protoanemonin [XXV] (A. Kockemann, Ber.deutsch.Bot.Ges.,1934,52,523; L. J. Haynes, loc.cit.) may be shown by a compound possessing an analogous structure such as dehydrocarolic acid [XXIII]. It would seem in many cases that the occurrence of the tetronic acid system is intimately bound up with that of sugar derivatives (e.g. Ascorbic acid and the metabolic products from P. Charlesii) but the mechanism of their production and their role in metabolism is at present a matter for conjecture.

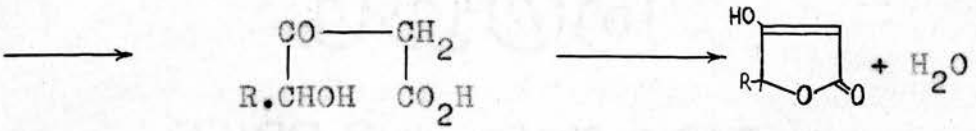
EXPERIMENTAL

THE SYNTHESIS OF TETRONIC ACIDS.

The methods which have been used for the synthesis of tetronic acids are summarised in the introduction to this thesis, but as a method which gave a good yield from easily available starting materials was required, few of these appeared satisfactory. Some were repeated for purposes of comparison, but recently exploited methods have enabled us to improve these earlier syntheses or to devise new ones.

The fundamental approach was to prepare a β-ketonic ester with a hydroxy or potential hydroxy group in the γ position and to cyclise this compound to the corresponding γ-lactone.

i.e. $R.CHOR'.CO.CH_2CO_2C_2H_5$



The alternative method was to take a γ-lactone containing a group in the β-position which could be converted in some manner to a ketonic function.

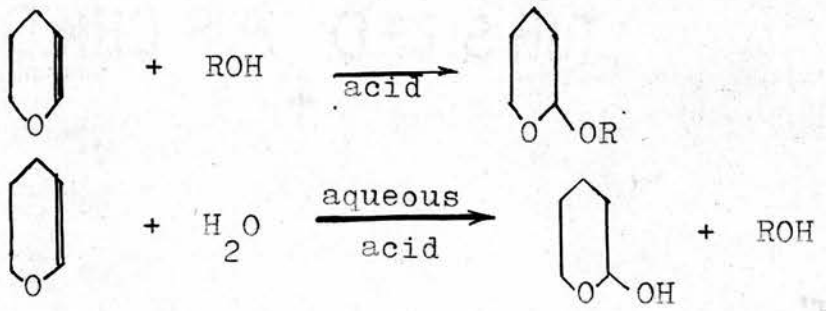
The first method of approach was made easier by the property of β-keto esters, which carry a chloro, a bromo or an acetoxy group in the γ-position and also an α-substituent, whether electron attracting or repelling, of cyclising spontaneously on standing in the cold, or more quickly on heating, to form a substituted

tetronic acid by loss of ethyl halide or ethyl acetate. The presence of an ∝-substituent appears necessary as attempts to cyclise γ-bromo-acetoacetic ester have been unsuccessful (A. H. Stanners, private communication, F. Reuter and R. B. Welch, J.Proc.Roy.Soc.N.S.Wales, 1939,72,120). The mechanism of this cyclisation has been previously discussed (Introduction; p.32) ∝-γ-dibromoacetoacetic ester readily undergoes loss of ethyl bromide to give ∝-bromotetronic acid, and this preparation due to L. Wolff (Ann.,1896,291,226) was repeated. To ethyl acetoacetate in ethereal solution was added the theoretical quantity of bromine, the reaction vessel being cooled. After washing to remove hydrogen bromide, the crude ester was heated for 2 hours on an oil bath at a temperature of 120-130° under diminished pressure. On cooling ∝-bromotetronic acid was deposited as brownish crystals and the liquid was filtered. A further quantity of less pure crystalline acid was obtained by heating the dark brown filtrate for a longer period under diminished pressure. The total yield by this method was 47% of an impure product which was difficult to purify by recrystallisation.

The method of E. Benary (Ber.,1907,40,1080), who prepared ∝-carbethoxy tetronic acid by condensation of chloracetyl chloride with sodio-malonic ester in ethereal suspension, was repeated but with little success, and

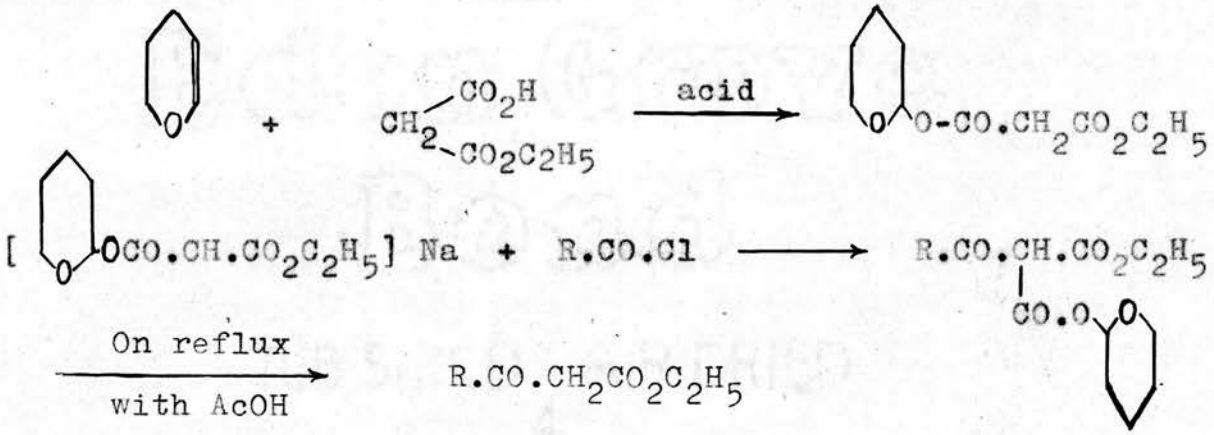
much highly coloured material was formed, which indicated that a number of competing reactions occur.

This type of synthesis was modified in order to produce the required type of intermediate by use of an α-acetoxy acid chloride in place of the α-chloro compound, and this was condensed with the sodio derivative of ethyl tetrahydropyranyl malonate. The tetrahydropyran group has been found useful for protection of hydroxyl groups under alkaline conditions (G. F. Woods and D. N. Kramer, J.Am.Chem.Soc., 1947, 69, 2246). It was found by R. Paul (Bull.Soc.Chim., 1934, [V], M., 1, 971) that 2:3-dihydropyran reacted with alcohols at room temperature in presence of a trace of acid to give a tetrahydropyranyl ether in good yield. This ether contains an acetal linkage which is stable under alkaline conditions but can readily be split by acids under mild conditions.



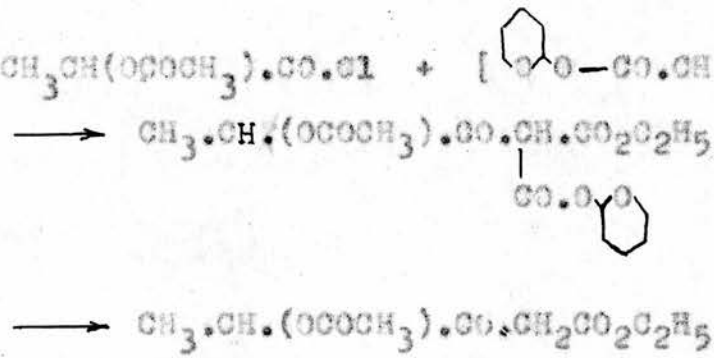
R. E. Bowman and W. D. Fordham, (J.Chem.Soc., 1952, 3945) had found that β-keto esters could be prepared in good

yield by reaction of an acid chloride with the sodio derivative of ethyl tetrahydropyranyl malonate to give an intermediate, not isolated, but which, on boiling under reflux in the presence of acetic acid, decarboxylated spontaneously to give a β-ketonic ester. Ethyl tetrahydropyranyl malonate was formed by the reaction of ethyl hydrogen malonate and 2:3-dihydropyran at room temperature in presence of a trace of acid, and this ester reacted with sodium in the same manner as diethyl malonate.

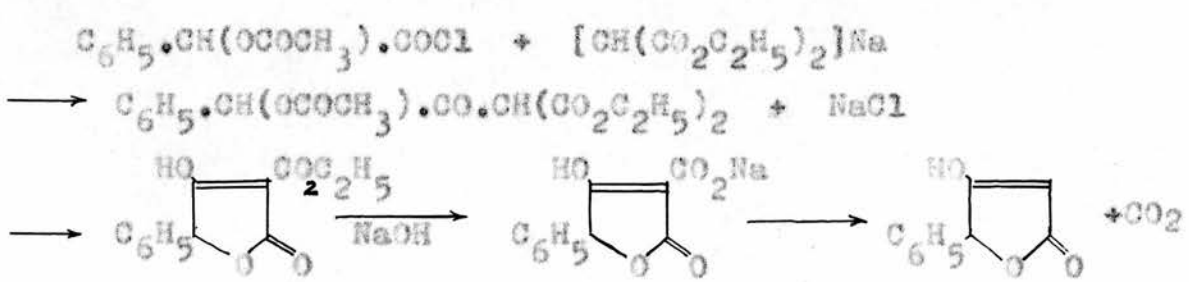


Acetyl lactic acid (β-acetoxy propionic acid) chloride was used as the acidic component and this was condensed with the sodio derivative of ethyl tetrahydropyranyl malonate. However, after decarboxylation the product would not distil without extensive decomposition.
A liquid which gave a red ferric chloride colour and and had $\lambda_{max.}$ 2350A. as might be expected for ethyl

γ-acetoxy-propionyl acetate, was obtained in 43% yield but was found to be analytically impure, even after careful redistillation in a short path distillation apparatus. An attempted hydrolysis of this liquid by alkali was unsuccesful and only decomposition products were isolated.



A repetition of the method of R. Anschütz and R. Böcker (Ann.,1909,368,53) for the synthesis of γ-phenyl tetronic acid was more successful. Condensation of acetyl mandelyl chloride with the sodio derivative of diethyl malonate in ethereal suspension, produced a yellow oil which on hydrolysis gave γ-phenyl tetronic acid:



A much improved yield was obtained by a method which was found generally applicable and which was not complicated by side reactions. H. Lund (Ber., 1934,67,935) had found that magnesium and dry ethanol (in presence of a little chloroform or carbon tetrachloride) would react with malonic ester to give a metallic derivative;

$$C_2H_5OH + Mg + CH_2(CO_2C_2H_5)_2 \longrightarrow (C_2H_5O)Mg.CH.(CO_2C_2H_5)_2 \quad 2/$$

and this would react with acid chlorides in the same manner as sodio-malonic ester but would not react with alkyl halides:-

$$R.CO.Cl + (C_2H_5O)Mg.CH.(CO_2C_2H_5)_2 \longrightarrow R.CO.CH.(CO_2C_2H_5)_2$$

This method has been adapted by several workers for the synthesis of β-keto esters (B. Riegel and W. M. Lilienfeld, J.Am.Chem.Soc.,1945,67,1273; M. Viscontini and N. Merckling, Helv.Chim.Acta,1952,35,2280).

For synthesis of tetronic acids this method has the advantage that, as alkyl halides do not react with the organometallic compound, an acid chloride containing an ∝-halogen atom may be used, thus eliminating some of the side reactions which occur in Benary's method described previously. Moreover, at no time is the

medium strongly alkaline.

For the synthesis of γ-phenyl tetronic acid acetyl mandelyl chloride in ethereal solution was added dropwise to the magnesio derivative prepared by reaction of magnesium ethoxide with the theoretical amount of malonic ester. Reaction, sufficient to promote steady reflux of the solvent, occurred without heating and a greenish white complex finally separated from the ether. After careful decomposition with ice, extraction and acidification, a yellow oil was obtained, which on standing eliminated ethyl acetate, cyclising to α-carbethoxy-γ-phenyl tetronic acid. When the oil was hydrolysed with approximately 1.25N alkali α-carbethoxy-γ-phenyl tetronic acid was obtained in good yield and this compound when boiled with 2N alkali followed by acidification of the solution, gave γ-phenyl tetronic acid, presumably by spontaneous decarboxylation of the unknown α-carboxylic acid, as carbon dioxide was evolved on addition of mineral acid. γ-Phenyl tetronic acid was recrystallised from water and had m.p.128°, and possessed the properties of a typical tetronic acid as described by R. Anschütz and R. Böcker (loc.cit.). By this method γ-phenyl tetronic acid could be prepared in 65% yield.

This method was extended to the synthesis of tetronic acid and to carolinic acid, a mould metabolite, which has

been discussed in the introduction to this thesis. This confirmed the structure of the latter compound as a γ-methyl tetronic acid bearing an α-(β-carboxypropionyl) substituent. (P. W. Clutterbuck, H. Raistrick and F. Reuter, Bio-chem.J.,1934,28,94; 1935,29,300,811,1300).

By reaction of β-ethoxycarbonyl propionyl chloride with ethylmagnesio malonate according to the directions of B. Riegel and H. M. Lilienfeld (loc.cit.), ethyl β-keto-α-carbethoxyadipate was obtained. This ester was hydrolysed to β-ketoadipic acid by keeping it at room temperature with concentrated hydrochloric acid for 36 hours (U. Eisner, J. A. Elvidge and R. P. Linstead, J.Chem.Soc.,1950,2223). The acid was then esterified by standing at room temperature in absolute ethanol saturated with hydrogen chloride. (S. F. Macdonald, J.Chem.Soc.,1952,4176). The ethyl β-ketoadipate was then reacted with magnesium ethoxide in dry benzene and the ethanol produced was removed azeotropically with benzene. The solution of the magnesium derivative [I] was reacted with DL-α-chloropropionyl chloride. Cautious treatment with mineral acid and extraction gave crude [II] which was then heated to effect cyclisation to [III]. Hydrolysis of the ester group in [III] with dilute sodium hydroxide solution at room temperature then gave DL-carolinic acid which crystallised from acetone/light petroleum in prisms m.p.137° and formed

a 2:4-dinitrophenylhydrazone m.p.228°. The naturally occurring (dextrorotatory) material has m.p.129° and forms a 2:4-dinitrophenylhydrazone m.p.228° (P. W. Clutterbuck, H. Raistrick and F. Reuter, loc.cit.). The synthetic material analysed correctly and was identical with natural carolinic acid in its ultra-violet spectrum and in its behaviour on paper chromatography in three different solvent systems. With ferric chloride in neutral solution, the synthetic and natural materials gave identical orange colours which were not altered by the addition of concentrated hydrochloric acid.

$$C_2H_5O_2C.CH_2CH_2CO.Cl + (C_2H_5O)Mg.CH(CO_2C_2H_5)_2$$

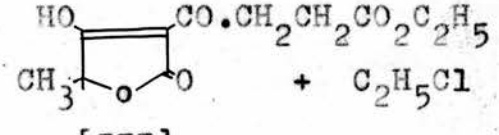
$$\longrightarrow \quad C_2H_5O_2C.CH_2CH_2CO.CH.(CO_2C_2H_5)_2$$

$$\xrightarrow{\text{conc. HCl}} \quad HO_2C.CH_2CH_2CO.CH.CO_2H \quad \xrightarrow{\text{EtOH/HCl}}$$

$$C_2H_5O_2C.CH_2CH_2CO.CH_2CO_2C_2H_5 \quad \xrightarrow{\text{EtOH/Mg}}$$

$$(C_2H_5O)Mg.\underset{\displaystyle CO_2C_2H_5}{CH}.CO.CH_2CH_2CO_2C_2H_5 \quad [I] \quad \xrightarrow{CH_3COCl}$$

$$\underset{\displaystyle CH_3CHCl}{CO}\!\!-\!\!\underset{\displaystyle CO_2C_2H_5}{CH}.CO.CH_2CH_2CO_2C_2H_5 \quad [II] \longrightarrow$$



$$+ \; C_2H_5Cl$$

[III]

Another approach to the synthesis of tetronic acids seemed to lie in reactions of the Claisen type, which had already been used for the synthesis of a potential precursor, ethyl γ-ethoxy acetoacetate (C. Weizmann, H. Stephen and G. S. Agashe, J.Chem.Soc.,1913,1855, T. B. Johnson and L. H. Chernoff, J.Am.Chem.Soc.,1914, 36,1742). The employment of the tetrahydropyranyl group for protection of the hydroxy group under alkaline conditions has already been described and the use of this group which can easily be removed appeared to increase the value of the Claisen condensation for syntheses of tetronic acids.

As a model experiment the self condensation of ethyl tetrahydropyranyloxyacetate was attempted. This ester was prepared by reaction of ethyl glycollate with 2:3-dihydropyran in presence of a trace of hydrochloric acid or an acid ion exchange resin.

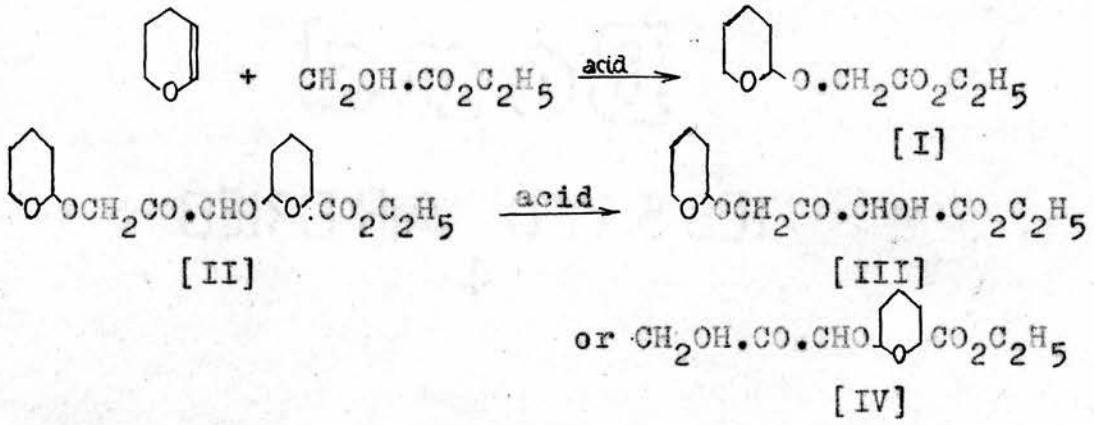
Condensation was effected by the action of sodium (1mol.) on the ester in ethereal solution under nitrogen at room temperature followed by a short period of heating. Unreacted sodium was destroyed by addition of ethanol. Decomposition and acidification of the brown sodio complex was carried out at 0° with aqueous tartaric acid. The product was ether extracted and by distillation on a short path distillation apparatus was separated into three fractions:-

(1) B.p. 60°/0.05mm

(2) B.p. 60-110°/0.05mm

(3) B.p. 110-120°/0.05mm

Fraction (1) was unchanged starting material. Fraction (2) was probably ethyl γ-hydroxy-α-tetrahydropyranyloxyacetoacetate [IV] or ethyl α-hydroxy-γ-tetrahydropyranyloxyacetoacetate [III], which arose by loss of a tetrahydropyranyl group from the expected product [Fraction (3)] on acidification. Fraction (3) a yellowish viscous liquid analysed correctly for ethyl 1:3-bis-(2'-tetrahydropyranyloxy)-2-ketobutyrate[II].

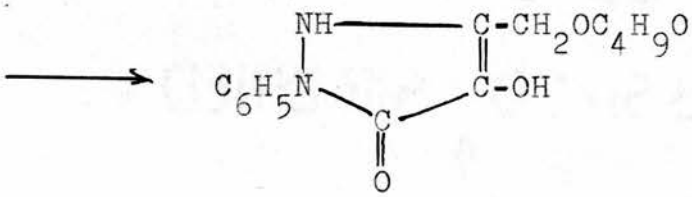


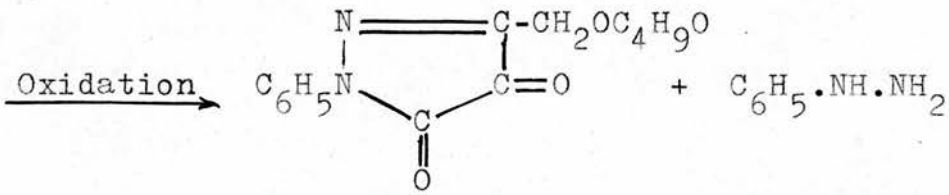
The compound [II] gave a purple ferric chloride colouration and slowly gave a purple colour on the addition of two drops of saturated aqueous o-dinitrobenzene indicating the presence of an ene-diol system (W. R. Fearon and E. Kawerau, Biochem.J.1943,37,326) formed by

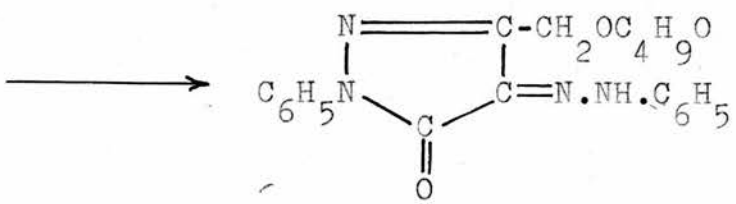
ready hydrolysis of a tetrahydropyranyl residue. When an attempt was made to prepare a pyrazolone from [II] and phenylhydrazine, the compound had m.p.123° and was bright orange. The analysis corresponded to the formula $C_{21}H_{22}O_3N_4$ [V] which might be expected if after loss of a tetrahydropyranyl residue and oxidation (as occurs in formation of the bis phenylhydrazone of hydroxytetronic acid) the original pyrazolone had condensed with a second molecule of phenylhydrazine.

CH_2OⓅ.CO.CHOⓅ.$CO_2C_2H_5$ (II) + $C_6H_5.NH.NH_2$

(Where Ⓟ = 2'-tetrahydropyranyl)







[V]

In an attempt to prepare hydroxytetronic acid hydrolysis of the ester was carried out under mildly acidic conditions and gave a yellow syrup, which was easily oxidised and on a paper chromatogram was found to give a spot possessing an R_F value (ascorbic acid as standard) greater than that of hydroxytetronic acid, and which unlike ascorbic acid, would only reduce the 2:6-dichlorophenol indophenol blue used as spray, after a preliminary spray with sodium bicarbonate solution. A very small spot, of the same R_F as would be expected for hydroxytetronic acid and which reduced 2:6-dichlorophenol indophenol blue under acidic conditions, was also observed.

The material was further hydrolysed with concentrated hydrochloric acid to give a brown syrupy substance which gave a single spot on a chromatogram, R_F = 0.66 (L. Mapson and S. M. Partridge, Nature,1949,164,479 give for hydroxytetronic acid R_F = 0.63); R_A = 0.17 (R_A measured relative to ascorbic acid = 0.17, Mapson and Partridge, loc.cit.).

This substance in one case crystallised but could not be recrystallised and readily turned dark brown. From it, was prepared a bis-phenylhydrazone which analysed correctly for the bis-phenylhydrazone of hydroxytetronic acid but which possessed a melting point lower than that quoted in the literature. (F. Micheel and F. Jung,Ber.,1934,67,1660).

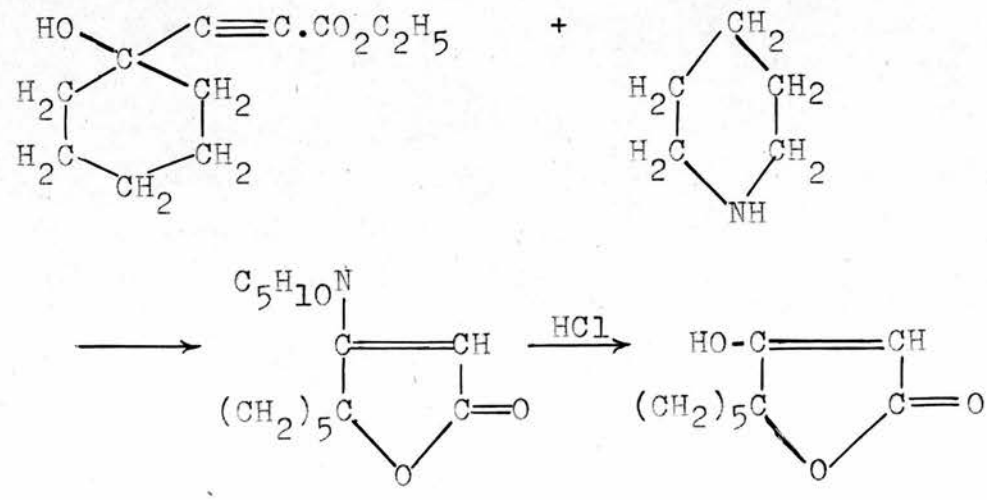
From alkaline hydrolysis of ethyl 1:3-bis-(2'-tetrahydropyranyloxy)-2-ketobutyrate, followed by acidification with tartaric acid and ether extraction, was obtained a yellow viscous oil, which gave no ferric chloride colour. After short path distillation the analysis corresponded to $C_{13}H_{22}O_5$ as would be expected for 1:3-di-(2'-tetrahydropyranyloxy) acetone. It proved difficult to obtain derivatives and p-nitrophenylhydrazine gave a material thought to be an osazone but which possessed a lower melting point than that recorded. (H. Dakin and H. Dudley, J.Biol.Chem., 1913, 15, 137). Acid hydrolysis gave a material possessing the properties of an ene-diol, which was examined by paper chromatography and although some indications of identity were observed when run against commercial 1:3-dihydroxy-acetone, the latter did not appear to be homogeneous but gave several spots.

(Ⓟ = 2'-tetrahydropyranyl)

$$CH_2O\text{Ⓟ}\ CO.CHO\text{Ⓟ}\ CO_2C_2H_5 \xrightarrow{NaOH} CH_2O\text{Ⓟ}\ CO.CHO\text{Ⓟ}\ .CO_2Na$$

$$\xrightarrow[acid]{} CH_2O\ \text{Ⓟ}.CO.CH_2O\text{Ⓟ} \quad + \quad CO_2$$

Another method of tetronic acid synthesis which was repeated as a convenient route to some tetronic acids required for light absorption studies, was that of E. R. H. Jones and M. C. Whiting (J.Chem.Soc.,1949, 1423). These authors found that with esters of γ-hydroxy-acetylenic acids, cis-addition of secondary aliphatic amines to triple bond occurred, usually exothermically, to give β-amino-αβ-ethylenic lactones, which were hydrolysed by heating with concentrated hydrochloric acid to tetronic acids. In our case one starting material was the ethyl ester of β-(1-hydroxycyclohexyl) propiolic acid and this reacted with piperidine in ethereal solution on standing at room temperature to give the lactone of β-N-piperidino-β-(1-hydroxycyclohexyl) acrylic acid. After heating on a steam bath with concentrated hydrochloric acid for 45 minutes and cooling, the lactone of β-hydroxy-β-(1-hydroxycyclohexyl) acrylic acid crystallised out.



EXPERIMENTAL SECTION.

Melting points are uncorrected. Micro-analyses are by Drs. Weiler and Strauss.

U.V. spectra were determined using a Unicam S.P.500 spectrophotometer. Absolute alcohol was purified by boiling under reflux with sodium and redistilled. Methanol was similarly treated. Water was glass distilled. Cyclohexane was B.D.H. Spectroscopic grade.

∝-Bromotetronic acid (L. Wolff and C. Schwabe, Ann., 1896,291,226).- Bromine (115.7g,83ml.) was added dropwise over 4 hours to a mixture of equal volumes of ether and ethyl acetoacetate (50g.). The reaction vessel was cooled under running water during the addition. When bromine addition was complete the mixture was left to stand overnight. It was then washed several times to remove hydrogen bromide and dried (Na_2SO_4). Solvent was removed and the brown (very lachrymatory) product was heated during 1.5 hours on an oil bath at a temperature of 120-130° and a pressure of 10-15mm. On cooling, brown crystalline ∝-bromotetronic acid (12g.31%) separated out and collected. The dark brown viscous filtrate was heated under the same conditions for 1.5 hours when more ∝-bromotetronic acid (6g.) crystallised. Total yield was 18g. (47%). When recrystallised from ethyl acetate the compound had m.p.183° (d.) (Wolff and Schwabe, (loc.cit.) give m.p.183°). With sodium nitrite solution the acid gave an intense purple colour in the cold. The crude acid was difficult to purify as it was only slightly soluble in ethyl acetate and treatment with charcoal in ethanol produced a dark brown solution which gave a tar on evaporation of solvent.

(with R. L. Cohen) ∝-Ethyltetronic acid.- Bromine (61.5g.) was added dropwise over a period of 2 hours to ∝-ethyl

ethyl acetoacetate (30.4g.) dissolved in an equal volume of ether contained in a reaction vessel cooled by running water. The ethereal solution was left to stand overnight, washed with water, dried (Na_2SO_4) and the solvent removed. The crude product was dissolved in xylene (100ml.) one drop of concentrated hydrobromic acid was added and the mixture was heated for 10 hours under reflux. On cooling, the addition of light petroleum precipitated a white solid (1.0g.) which was collected. By repeated heating and treatment with light petroleum a further quantity of dark coloured solid (2g.) was obtained.

The ∝-ethyltetronic acid (3.0g.10%) was recrystallised from ethyl acetate m.p.126-127°. W. Wedel (Ann.,1883, 219,71) reports m.p.126.5°.

∝∝-Diethyl tetronic acid (cf. E. B. Reid, R. B. Fortenbaugh and H. R. Patterson,J.Org.Chem.,1950,15,572).

i) Ethyl ∝∝-diethyl-γ-bromoacetoacetate.- Bromine (16g.) was added dropwise during 6 hours to an ice cooled mixture of ethyl ∝∝-diethylacetoacetate (18.6g.) and dry ether (15ml.). When the mixture had stood overnight it was diluted with ether (50ml.), washed several times with water, dried (Na_2SO_4) and ether was removed. The crude bromo-compound, a brown oil, was used in the next stage without purification.

ii) Ethyl ∝∝-diethyl-γ-acetoxy-acetoacetate.- Crude ethyl ∝∝-diethyl-γ-bromoacetoacetate (26.1g.) was dissolved in an equal volume of ethanol and mixed with a solution of anhydrous potassium acetate (14g.) in absolute ethanol (100ml.). The mixture was heated for 1.5 hours on a water bath under reflux. Potassium bromide (7.7g. theoretical 11.7g.) separated. When cool the mixture was filtered and to the filtrate was added water (200ml.) and the mixture was extracted with ether. The extract was dried (Na_2SO_4) and ether removed. A brown liquid (17.55g.) remained.

iii) Cyclisation of ethyl ∝∝-diethyl-γ-acetoxyacetoacetate.- The brown liquid (17.55g.) from acetolysis of the bromo ester, was added slowly to concentrated sulphuric acid (35ml.) with cooling during 30 minutes. The dark brown mixture was kept for 48 hours at 0° and then poured on to ice (200g.). The liquid was extracted with chloroform, and the extract dried (Na_2SO_4) and solvent was removed. It was redistilled and had b.p.51°/0.1mm. n_D^{15} 1.4470. The yield was 7g. (42%) M. Conrad and R. Gast (Ber.,1898,31,2954) give b.p.219-225°.

A semicarbazone was obtained by reacting the lactone (0.5g.) with semicarbazide acetate solution. [The latter was prepared from semicarbazide hydrochloride (0.5g.) dissolved in the minimum quantity of warm water,

added to potassium acetate (2g.) dissolved in the minimum quantity of warm methanol and the mixture cooled and filtered.] The reagents were heated for 25 minutes on a water bath, water was added and the mixture was left overnight when the compound crystallised and was collected. ∝∝-Diethyl-β-keto-γ-butyrolactone semicarbazone crystallised from absolute ethanol as colourless prisms, m.p.175°. (Found C,50.7%; H,7.25%; N,19.2%. $C_9H_{15}O_3N_3$ requires C,50.7%; H,7.1%; N,19.7%)

Attempted preparation of ∝-ethoxycarbonyl tetronic acid by the method of Benary (Ber.,1907,40,1080).- Sodium ethoxide was prepared by dissolving sodium (41g.) in purified absolute ethanol (500ml.) under dry nitrogen. Excess ethanol was removed under diminished pressure and the residue was suspended in dry ether (250ml.). Diethyl malonate (280g.) dissolved in dry ether (250ml.) was added to the sodium ethoxide and the reaction was allowed to proceed at room temperature for one hour when a suspension of sodio malonic ester was formed.

To this suspension in a reaction vessel cooled in ice was slowly added a solution of chloroacetyl chloride (100g.) in dry ether (100ml.). A vigorous reaction took place and a bright yellow insoluble complex was formed. The mixture was heated on a water bath under reflux for 30 minutes and then left to stand overnight. It was impossible to filter the orange coloured complex according to the directions of Benary (loc.cit.) therefore to the mixture was added an equal volume of very dilute hydrochloric acid. The ether layer was separate but both it and the aqueous layer contained a large amount of red coloured solid in suspension. The ethereal solution was filtered and the solid was dissolved in chloroform. The aqueous layer was extracted with chloroform, the combined chloroform extract was dried (Na_2SO_4) and

solvent was distilled until the bulk was about 250ml. A dark red solid (2g.) separated and was collected. This when crystallised from ethanol proved to be a mixture of a dark red compound with green fluorescence and a more soluble pale yellow compound. Neither of the compounds possessed the properties of α-ethoxycarbonyl tetronic acid nor could any α-ethoxycarbonyl tetronic acid be obtained from them.

The remainder of the chloroform solution was evaporated under diminished pressure and some diethyl malonate was distilled off. The remaining solution was dark red, fluorescent and possessed a smell of diethyl malonate.

A similar dark red solution was obtained by evaporation of the ethereal extract previously separated from the aqueous layer after the reaction.

It appeared from the products of the reaction that the sodium ethoxide used must have contained ethanol and this factor, combined with the use of excess sodio malonic ester accounts for the recovery of malonic ester and the production of compounds which are probably derived from malonic ester by self condensation in presence of sodium ethoxide.

Modification of Bowman's method for preparation of β-keto esters. (cf. R. E. Bowman and W. D. Fordham, J.Chem.Soc., 1952,3945).

i) Potassium ethyl malonate.- (M. Freund, Ber.,1884,17,780) A solution of potassium hydroxide (17.4g.) in absolute ethanol (100ml.) was added dropwise to diethyl malonate (50g.) in absolute ethanol (100ml.). Addition was at such a rate that the solid which formed at every drop was dissolved by stirring the solution. The mixture was left to stand for 12 hours after the addition of alkali had been completed. The white crystals of potassium ethyl malonate were filtered under suction and dried in a desiccator.

ii) Ethyl hydrogen malonate.- (F. Marguery, Bull.Soc.chim., 1905,33,541). Potassium ethyl malonate (40g.) was dissolved in water (80ml.) and concentrated sulphuric acid (8ml.) was added very slowly to the solution. The liquid was extracted with ether (9 portions of 20ml.). The extract was dried (Na_2SO_4) and ether was evaporated off under diminished pressure. The residual liquid had b.p.88°/0.25mm. n_D^{15} 1.4285. The yield was 21g. (69%). R. E. Bowman (loc.cit.) reports b.p.101-2°/2mm. n_D^{20} 1.4295.

iii) α-Acetoxypropionyl chloride.- α-Acetoxy propionic acid (20g.) was heated for 1.5 hours under reflux with

purified thionyl chloride (30ml.). The mixture was left overnight and thionyl chloride was removed by distillation under diminished pressure. The acid chloride (17.6g.76%) had b.p.59°/18mm. R. Anschütz and W. Bertram (Ber.,1904, 37,3971) give b.p.56°/11mm.

iv) Condensation of α-acetyl propionyl chloride with the sodio derivative of ethyl 2'-tetrahydropyranyl malonate.- Ethyl hydrogen malonate (12g.) was added slowly to a solution of dihydropyran in (13g.) in dry benzene (20ml.) containing 2 drops of a 10% solution of 2:5-dichloro-benzoic acid in methanol. The temperature did not exceed 30°. The solution was left to stand 4 hours and then was shaken with solid potassium hydroxide (0.2g.) to remove free acid. When the solution had been decanted from inorganic material, excess dihydropyran and solvent were removed under diminished pressure. The residual ester in dry benzene (50ml.) was added to powdered sodium (2.09g.) in benzene (50ml.) with cooling. When the sodium had dissolved, acetoxy propionyl chloride (11g.) in dry benzene (20ml.) was added dropwise, and the reaction was left to stand for one hour at room temperature. Acetic acid (1ml.) was added and the solution was boiled under reflux for one hour. Carbon dioxide was evolved. The yellow precipitate of inorganic matter was removed by filtration and the orange liquid

was evaporated under diminished pressure to remove solvent. The residual liquid (18.5g.) was purified by fractional distillation and gave 2 fractions:

1) B.p. 57-63°/0.6mm. (6.25g.)

2) B.p. 90° /0.6mm. (0.5g.)

The main bulk of the material resinified in the distillation flask to a dark brown mass.

Fraction 1) had $\underline{n}_D^{18.5}$1.4420. Redistilled in a short path distillation apparatus it had $\underline{n}_D^{20}$1.4344. In ethanolic solution it gave a deep red colour with ferric chloride. The liquid was probably ethyl 3-acetoxy-propionylacetate but it was found to be analytically impure. It showed the expected light absorption properties in ethanol $\lambda_{max.}$ 2350A. ($\varepsilon_{max.}$ 1,700) shifted to $\lambda_{max.}$ 2630A. by the addition of sodium ethoxide.

Fraction 2) appeared to be a condensation product and gave no reaction in ethanolic solution with ferric chloride.

Preparation of phenyl tetronic acid by the method of Anschütz and Böcker (Ann.,1909,368,53)

i) Acetyl mandelic acid. (R. Anschütz and R. Böcker, loc.cit.).- Mandelic acid (100g.) was treated with acetic anhydride (100g.) containing concentrated sulphuric acid (0.5ml.). Reaction was immediate and the acid dissolved with evolution of heat. The solution was left to stand overnight and water (400ml.) was added. The acid crystallised and was sucked dry at the pump. The substance after drying over phosphorus pentoxide at 60° under diminished pressure had m.p.76°. R. Anschütz and R. Böcker (loc.cit.) report m.p.80°.

ii) Acetyl mandelyl chloride. (R. Anschütz and R. Böcker, loc.cit.).- The acid prepared above was dried by dissolving it in toluene and drying the solution (Na_2SO_4). Toluene was removed under diminished pressure to effect complete removal of water by azeotropic distillation. To the dried acid (a syrup) was added purified thionyl chloride (160g.). The mixture was heated under reflux for one hour and then left to stand overnight at room temperature. Excess thionyl chloride was removed by distillation under diminished pressure. Acetyl mandelyl chloride (124g.,89%) had b.p.92-95°/0.2mm. R. Anschütz and R. Böcker (loc.cit.) give b.p.129°/10mm.

iii) γ-phenyl tetronic acid.- (R. Anschütz and R. Böcker, loc.cit.). Ethyl malonate (11.30g.) was added to sodium wire (1.65g.) in dry ether (150ml.). The mixture was heated under reflux on a water bath until all the sodium had reacted. Acetyl mandelyl chloride (15g.) dissolved in twice its own volume of dry ether was added dropwise to the sodio derivative over a period of 2 hours with stirring. The reaction was left overnight and then the yellow complex was decomposed with ice and was acidified with a slight excess of dilute sulphuric acid. The organic layer was separated and the mixture was extracted with ether. The extract was dried (Na_2SO_4) and ether was evaporated under diminished pressure. A yellow oil remained which was hydrolysed by leaving it to stand for 2 days at room temperature with sodium hydroxide solution (16g. in 100ml.). The yellow solution was extracted with ether to remove unhydrolysed material and was then made acid with hydrochloric acid. Phenyl tetronic acid separated as an oil which was extracted with ether. The extract was dried (Na_2SO_4) and ether was evaporated under diminished pressure when crude phenyl tetronic acid (6g.,48%) crystallised. Recrystallised from hot water it had m.p.127°.

R. Anschütz and R. Böcker (loc.cit.) report m.p.127.5-128.5°.

Modification of Benary's synthesis of tetronic acids.

(with H. W. W. Ehrlich) Synthesis of ethyl γ-chloro-α-ethoxycarbonyl-β-oxo-butyrate.- Dry ethanol (25ml.) and carbon tetrachloride (0.5ml.) were added to pure magnesium (5g.) which had been washed with ether and vacuum dried. When the first vigorous reaction had subsided, dry ethanol (11ml.) was added and the mixture was heated under reflux on a boiling water bath for 1 hour. It was left overnight and redistilled diethyl malonate, (33.76g.,32ml.) was added. Solution of magnesium was completed by heating on a water bath for 1 hour, the complex was dissolved in dry ether (75ml.) and the solution cooled in ice. Chloroacetyl chloride (25g.,17ml.) in ether (17ml.) was added gradually and then the mixture was heated under reflux for 30 minutes. Ice was added to decompose the complex which was then made acid with dilute sulphuric acid. The ether extract was dried (Na_2SO_4) and after removal of ether a yellow oil (30g.) remained.

The yellow oil was found to contain 14.30% chlorine. When it was distilled, diethyl malonate was first obtained b.p.85°/10mm., followed by a small quantity of ethyl γ-chloro-α-ethoxycarbonyl-β-oxo-butyrate, a clear liquid b.p.130-133°/10mm. n_D^{10} 1.4648. Analysis showed that the liquid contained 14.95% chlorine ($C_9H_{13}O_5Cl$

requires 14.99% chlorine). It was found that only a little of this compound could be obtained by distillation, as decomposition occurred in the apparatus with formation of a solid identified as α-ethoxycarbonyl tetronic acid.

α-Ethoxycarbonyl tetronic acid.- The impure chloroacetyl malonic ester (25g.) was heated under reflux in xylene (30ml.) for 2 hours. On cooling, followed by addition of petroleum ether (b.p.40-60°), α-ethoxycarbonyl tetronic acid (7.5g.) was precipitated. Recrystallised from ethyl acetate and dried, it formed colourless prisms m.p.125°. E. Benary (Ber.,1907,40,1080) gives m.p.124-5°.

Tetronic acid.- α-Ethoxycarbonyl tetronic acid (1.5g. m.p.116°) was hydrolysed by boiling under reflux with sodium hydroxide solution (1.2g. in 12ml. water) for 45 minutes. The solution was cooled and acidified with sulphuric acid (4ml. of 1:3, concentrated acid/water). Organic material was extracted 6 times with ethyl acetate (20ml. portions). The extract was dried (Na_2SO_4) and when solvent was removed under diminished pressure the tetronic acid (0.4g.57%) crystallised and had m.p.134°. It crystallised from ethyl acetate as colourless prisms m.p.138°. L. Wolff and C. Schwabe (loc.cit.) report sintering 135°, m.p.141°.

With ferric chloride solution it gave a red colour and with sodium nitrite solution it gave an intense purple colour.

O-Benzoyl tetronic acid.- Tetronic acid (0.2g.) was dissolved in sodium carbonate solution (15ml.) and was shaken for 20 minutes in a corked flask with benzoyl chloride (1g.). When the mixture had stood overnight the solid was filtered off, washed with warm water and dried. After recrystallisation twice from chloroform/light petroleum (b.p.60-80°) O-benzoyl tetronic acid crystallised as colourless prisms m.p.120°. L. Wolff and C. Schwabe (loc.cit.) give m.p.120°.

Synthesis of Carolinic Acid.

i) Ethyl hydrogen succinate (B. Riegel and W. M. Lilienfeld, J.Am.Chem.Soc.,1945,67,1273).- To succinic anhydride (100g.) was added dry ethanol (120ml.). The mixture was heated under reflux on an oil bath (110°) until the ethanol ceased to boil. Solid succinic acid (ca.5g.) separated and was removed by filtration. Excess ethanol was distilled off. The crude half-ester, a colourless oil, was used in the next stage without further purification.

ii) β-Ethoxycarbonyl propionyl chloride (B. Riegel and W. M. Lilienfeld loc.cit.).- To the above ethyl hydrogen succinate was added redistilled thionyl chloride (120ml.) and the reagents were heated under reflux for 1 hour.

When the solution had stood overnight excess thionyl chloride was removed by distillation under diminished pressure and the acid chloride (119.2g.72%) distilled as a colourless liquid b.p. 96-100°/20mm.$n_D^{16.5}$1.4340. B Riegel and W. M. Lilienfeld (loc.cit.) give b.p. 110-115°/30mm.

iii) Ethyl α-ethoxycarbonyl-β-Ketoadipate (B. Riegel and W. M. Lilienfeld loc.cit.).- To pure magnesium (15.5g.), dry ethanol (15ml.) and carbon tetrachloride (1ml.) were added redistilled diethyl malonate (99.36g.) and dry ethanol (50ml.) in dry ether (200ml.). The mixture was heated 10 hours under reflux to complete solution of magnesium to give a dark green syrup which was freed from ether and ethanol by distillation under diminished pressure. Final removal of ethanol was ensured by addition of dry benzene (200ml.) which dissolved the syrup and was then evaporated under diminished pressure.

The syrupy magnesio-derivative was dissolved in dry ether (300ml.) and to it was added dropwise with stirring β-ethoxycarbonyl propionyl chloride (71.9g.) dissolved in its own volume of ether, at a rate to produce steady boiling of the solvent. The mixture was then heated under reflux for 3 hours, left overnight and heated a further 1.5 hours. The viscous complex which had separated was

decomposed by slow addition of ice cold sulphuric acid (19ml. concentrated acid in 250ml. water). The aqueous layer was extracted with ether, the extract was dried (Na_2SO_4) and ether was removed under diminished pressure. The liquid was distilled at the oil pump, a fore-run of ethyl malonate was collected, and ethyl ∝-ethoxycarbonyl-β-ketoadipate (124g.56%) distilled at 137-141°/0.15mm. n_D^{13}1.4527. U. Eisner, J. A. Elvidge and R. P. Linstead (J.Chem.Soc.,1950,2223) give n_D^{20}1.4506 and b.p.144°/0.2mm.

Ethyl ∝-ethoxycarbonyl-β-ketoadipate (0.5g.) was warmed to boiling with p-nitrophenylhydrazine (1.0g.) in ethanol (30ml.) concentrated hydrochloric acid (1ml.) was added and the solution was boiled for 2 minutes. The red solid was collected on cooling. 3-(2-ethoxycarbonylethyl)-4-ethoxycarbonyl-1-p-nitrophenyl-5-pyrazolone crystallised from aqueous ethanol as brownish prisms m.p.112°. (Found C,54.45%; H,4.95%. $C_{17}H_{19}O_7N_3$ requires C,54.10%; H,5.0%.).

iv) Attempted reaction of ethyl ∝-ethoxycarbonyl-β-ketoadipate with magnesium ethoxide.- Magnesium ethoxide was prepared by reaction of pure magnesium (1.025g.) with dry ethanol (10ml.) and carbon tetrachloride (0.5ml.) at room temperature and the reagents were left to stand for 20 hours after the first vigorous reaction had subsided.

To the ethoxide dissolved in dry ether (50ml.) was added ethyl ∝-ethoxycarbonyl-β-ketoadipate (15g.) in dry ether (40ml.) and the mixture was heated under reflux after adding a little more ethanol to react with excess magnesium. When the magnesium had dissolved solvent and excess ethanol were removed as in the previous experiment.

The yellow syrup remaining was dissolved in dry ether (50ml.) and the ∝-chloropropionyl chloride (5.4g.) in dry ether (50ml.) was added dropwise with stirring. Reaction occurred with separation of white solid, the liquid was heated under reflux during 1 hour and a white complex separated which was left overnight. This was decomposed by addition of cold water and acidified with sulphuric acid (2ml. concentrated acid in 100ml. water). The mixture was extracted with ether, the extract was dried (Na_2SO_4) and solvent removed. A green liquid (15g.) remained which in ethanol gave a red colour with ferric chloride and had $n_D^{11.5}$ 1.4522. This liquid was found to be unchanged ethyl ∝-ethoxycarbonyl-β-ketoadipate.

This was confirmed by preparation of a pyrazolone derivative as described in the preceding section. No depression of m.p. was observed on mixed melting point determination with the compound prepared from authentic ethyl ∝-ethoxycarbonyl-β-ketoadipate.

v) Hydrolysis of ethyl α-ethoxycarbonyl-β-ketoadipate (U. Eisner, J. A. Elvidge and R. P. Linstead, J.Chem.Soc., 1950,2223).- The ester (24g.) was left to stand in the cold with concentrated hydrochloric acid (70ml.) for 40 hours. Carbon dioxide was evolved. Most of the solvent was removed on a water bath below 35° under diminished pressure. The partly crystalline residue was left to stand in a vacuum desiccator over calcium chloride and potassium hydroxide pellets to remove hydrogen chloride. The yield of acid was 10.8g. (80%) and it had m.p.117°. U. Eisner, J. A. Elvidge and R. P. Linstead (loc.cit.) give m.p.116° and state that the acid required no further purification.

vi) Esterification of β-ketoadipic acid (S. F. Mcdonald, J.Chem.Soc.,1952,4176;cf. 'Organic Syntheses', Coll.Vol.I p.126).- Absolute ethanol (35ml.) was saturated with dry hydrogen chloride. To this the above dry β-ketoadipic acid (32g.) was added and the mixture was warmed on a water bath at 45° until the acid dissolved. The reagents were allowed to stand at room temperature for 12 hours and then poured on to ice water (100ml.). The solution was extracted twice with benzene (50ml. portions), washed once with 10% sodium carbonate solution (30ml.), washed once with dilute sulphuric acid (30ml.) and was finally washed twice with water (30ml. portions).

Benzene was removed on the water bath and ethyl β-ketoadipate (16g.) distilled over at 109°/0.2mm. n_D^{17} 1.4405.

vii) Ethyl 6-chloro-3:5-dioxo-4-ethoxycarbonyl-octoate.- Ethyl β-ketoadipate (16g.) was added to a solution in dry benzene (50ml.) of magnesium ethoxide prepared as previously described from pure magnesium (1.75g.). When the vigorous reaction had subsided, solution of magnesium was completed by heating the mixture under reflux on a water bath. Benzene was removed under diminished pressure and the green syrup was dissolved in dry benzene (100ml.) which was again removed under diminished pressure to effect complete azeotropic distillation of ethanol. α-Chloropropionyl chloride (9.5g.) in dry benzene (25ml.) was added slowly to a solution of the syrup in dry benzene (100ml.). No immediate reaction was observed but separation of a green viscous complex took place on warming. The mixture was heated for 2 hours under reflux on a water bath and left to stand overnight. It was heated for a further hour, cooled and decomposed with ice water. Sulphuric acid (4ml. concentrated acid in 50ml. of water) was added and the organic layer was extracted with ether, the combined extracts were dried (Na_2SO_4) and solvent was removed under diminished pressure. The yellow liquid remaining gave an orange red colour with ferric chloride. n_D^{16} 1.4740. The crude ethyl 6-chloro 3:5-dioxo-4-ethoxycarbonyl-octoate was used in the next

stage without purification.

viii) Cyclisation of ethyl 6-chloro-3:5-dioxo-4-ethoxy-carbonyl-octoate to the ethyl ester of carolinic acid.-
i) When the compound was left to stand at room temperature for some weeks, cyclisation occurred spontaneously and the product was shown to contain no chlorine. Crude ethyl carolinate was thus obtained as a yellow oil which gave an orange red ferric chloride colour.
ii) The compound (5g.) was heated on an oil bath at 120° and pressure of 25mm. for 3 hours. Cyclisation took place with very little darkening of the liquid, crude ethyl carolinate being obtained as a yellow oil.

ix) Carolinic acid.- The cyclised ester (10g.) was left to stand at room temperature 48 hours with sodium hydroxide solution (4g. in 200ml. water). The solution was extracted with ether (60ml.) and then acidified to pH 3 with dilute hydrochloric acid. When this solution was extracted with ether, β-keto-adipic acid (0.1g.) was obtained. The aqueous solution was then continuously extracted for several working days with ether. The extracts were removed and carolinic acid was obtained as white crystals together with an orange oil, which deposited more crystalline acid on ether treatment. The crystals were collected and washed with

ether. The total yield was 0.95g. The crude acid had m.p.116° and recrystallised from ethyl acetate as colourless prisms m.p.137.5°. When the crude compound was allowed to solidify, on reheating it had m.p.134°. (Found: C,50.45%; H,4.75%. $C_9H_{10}O_6$ requires C,50.45%; H,4.70%).

Both the synthetic and natural carolinic acid gave an orange colour with ferric chloride in aqueous solution, stable to strong hydrochloric acid. In this respect it resembles the orange colour produced by α-acetyl-γ-phenyl tetronic acid with ferric chloride. Carolinic acid was titrated against 0.1N sodium hydroxide using phenolphthalein indicator and its equivalent was found to be 113.($C_9H_{10}O_6$ dibasic, requires equivalent of 107). Light absorption in water showed $\lambda_{max.}$ 2300 A. ($\varepsilon_{max.}$ 16,800) and 2620 A. ($\varepsilon_{max.}$ 16,800). R. W. Herbert and E. L. Hirst (Biochem.J.,1935,39,1881) give $\lambda_{max.}$ 2650 ($\varepsilon_{max.}$ 13,800) and 2300 A. ($\varepsilon_{max.}$ 12,600).

2:4-Dinitrophenylhydrazone of carolinic acid.- 2:4-Dinitrophenylhydrazine (50ml. of a solution containing 10g./l. in dilute sulphuric acid) was added to carolinic acid (0.1g.) in aqueous solution. A precipitate began to form within 15 minutes and the solution was left to stand overnight at room temperature to allow completion of the reaction. Carolinic acid 2:4-dinitrophenylhydrazone was collected, washed with ethanol and dried. It had

m.p.224° (d) which rose to 228-229° (d.) after recrystallisation from nitrobenzene/toluene. P. W. Clutterbuck, H. Raistrick and F. Reuter (Biochem.J.,1935,29,300) report m.p.228°. (Found:- C,46.7%; H,3.75%; N,13.9%. $C_{15}H_{14}N_4O_9$ requires C,45.7%; H,3.6%; N,14.2%).

Examination of synthetic carolinic acid by paper chromatography.- The following solvent systems were used:-

i) Ethanol/ammonia (0.880)/water, (80:4:16,v./v.).

ii) isoPropanol/water, (90:10,v./v.).

iii) Butanol/glacial acetic acid/water, (40:10:50,v./v.).

iv) Propanol/ammonia (0.880)/water, (50:25:25,v./v.).

When the paper had been irrigated for 20 hours using one of the above solvent systems, it was dried and sprayed with aqueous ferric chloride solution. An orange spot was observed against a pale yellow background. Authentic dl-carolinic acid (supplied by Professor E. L. Hirst), ∝-bromotetronic acid, and ∝-carbethoxy tetronic acid were used for comparison with synthetic carolinic acid. The results obtained are tabulated.

Table of R_F values.

Solvent	Carolinic acid (Natural).	Carolinic acid (Synthetic)	∝-Bromo-tetronic acid.	∝-Carbethoxy tetronic acid.
	R_F	R_F	R_F	R_F
(i)	0.49	0.49	-	0.83
(ii)	0.39	-	0.58	0.58
(iii)	0.5	0.5	0.5	-
(iv)	0.68	-	0.84	0.84
(iv)	0.60	0.60	0.79	-

It was found that in all the solvent systems used ∝-bromotetronic acid and ∝-carbethoxy tetronic acid possessed the same R_F value, as did synthetic and natural carolinic acid. From the above values a comparison of the behaviour of the synthetic material with that of natural carolinic acid aids in confirming their identity, already established on the basis of chemical properties and ultra-violet light absorption data.

<u>α-Ethoxycarbonyl-γ-phenyl tetronic acid.-</u> Redistilled diethyl malonate (40g.) in dry ether (100ml.) was added to magnesium ethoxide, prepared from pure magnesium (6.08g.), in dry ether (200ml.). The mixture was heated under reflux for 30 minutes and left to stand overnight at room temperature. Excess ethanol was removed by azeotropic distillation with toluene (150ml.) which was removed under diminished pressure. This was repeated and the resulting green syrup was dissolved in dry ether (150ml.). Acetyl mandelyl chloride (53.1g.) mixed with dry ether (60ml.) was added to the solution with stirring at such a rate that the solvent boiled gently. During the reaction a white precipitate occasionally appeared and redissolved on stirring, but when addition of acid chloride was almost complete, the precipitate separated to form an insoluble greenish white syrup. The reaction was left overnight at room temperature and the mixture was then heated for 30 minutes on a water bath under reflux.

The complex was decomposed by the addition of ice (150g.) and 30 minutes later it was acidified with sulphuric acid (17ml. concentrated acid in 23ml. water) added with careful mixing. The ethereal layer was separated and the aqueous layer was extracted with ether. The combined ethereal extract was dried (Na_2SO_4), ether was evaporated under diminished pressure and a yellow

oil remained (91g.). The oil was hydrolysed with sodium hydroxide solution (40g. in 250ml. water). The mixture was left standing for 3 days at room temperature. It was then made acid with strong sulphuric acid (concentrated acid diluted with twice its own volume of water). The precipitate was collected and sucked dry at the pump. It was dissolved in chloroform, the solution was dried (Na_2SO_4) and most of the chloroform, was distilled. The remaining solution was poured into a basin and solvent was evaporated in a desiccator under diminished pressure. A cream coloured solid (42.5g.) was obtained which was identified as α-ethoxycarbonyl -γ-phenyl tetronic acid containing a large amount of γ-phenyl tetronic acid.

α-Ethoxycarbonyl-γ-phenyl tetronic acid recrystallised from ethyl acetate or ethanol as prisms m.p.145°. R. Anschütz and R. Böcker (loc.cit.) give m.p.140° (Found C,62.3%; H,4.65%. $C_{13}H_{12}O_5$ requires C,62.9%; H,4.85%).

γ-Phenyl tetronic acid.- The above crude solid (20g.) was hydrolysed by boiling with sodium hydroxide solution (8g. in 100ml. water) for 45 minutes under reflux. The solution was cooled and acidified with concentrated hydrochloric acid when a cream coloured precipitate separated and was collected. More solid was obtained by

chilling the mother liquor. The solid was sucked dry and dried in a desiccator. Yield 13.5g. (65% based on acetyl mandelyl chloride). Recrystallised from water the compound had m.p. 127°. R. Anschütz and R. Böcker (loc.cit.) give m.p. 127.5-128.5°. Equivalent by titration with sodium hydroxide was found to be 177 ($C_{10}H_8O_3$ requires 176). With sodium nitrite solution the compound gave a blue colour and with ferric chloride solution it gave a red colour.

A 2:4-dinitrophenylhydrazone was prepared by heating a mixture of 2:4-dinitrophenylhydrazine (0.5g.) ind phenyl tetronic acid (0.25g.) in ethanol to boiling, when concentrated hydrochloric acid (0.5ml.) was added and the solution boiled for a further two minutes. Unchanged 2:4-dinitrophenylhydrazine crystallised on cooling and was removed by filtering the solution. On standing yellow crystals of γ-phenyl tetronic acid 2:4-dinitrophenylhydrazone were deposited. Crystallised from ethanol m.p.137°. (Found: C,53.3%; H,3.80%; N,15.6%. $C_{16}H_{12}O_6N_4$ requires C,53.5%; H,3.35%; N,16.2%.).

The methyl ether of γ-phenyl tetronic acid.- γ-Phenyl tetronic acid (0.5g.), methyl iodide (2g.) and 4N sodium hydroxide solution (0.7ml.) were added to methanol (3ml.). After 5 days the neutral fraction was isolated by ether extraction of the solution [to which water (5ml.) had been added] followed by washing the ether extract with bicarbonate solution. The extract was dried (Na_2SO_4) and the solvent was evaporated under diminished pressure. The product did not solidify, but extraction of the syrupy material with light petroleum (b.p.40-60°) gave the methyl ether as a colourless solid which crystallised from light petroleum (b.p.40-60°) as long rods m.p.96-97°. R. A. Raphael (J.Chem.Soc.,1949,118) gives m.p.98°.

γ-phenyl tetronic acid enol acetate.- i) γ-phenyl tetronic acid (2g.), isopropenyl acetate (10ml.) and 3 drops of a 10% methanolic solution of 2:5-dichlorobenzene sulphonic acid were heated for 30 minutes on a water bath. The mixture was left overnight at room temperature and acetone and excess isopropenyl acetate were removed under diminished pressure. A brown oil remained which solidified after several days. The oil was extracted with boiling light petroleum (b.p. 60-80°) and when the solution was cooled the γ-phenyl tetronic acid enol acetate was obtained as a light

yellow solid m.p.77.5° which on recrystallisation from light petroleum (b.p.60-80°) formed colourless needles, m.p.79.5°. (Found C,65.75%; H,4.6%. $C_{12}H_{10}O_4$ requires C,66.05% H,4.6%).

ii) γ-Phenyl tetronic acid (1.5g.) was ground with acetic anhydride (4ml.). Two drops of concentrated sulphuric acid was added and the mixture was warmed on a water bath for 30 seconds. The reaction was allowed to proceed at room temperature for 1.5 hours and then the mixture was dissolved in chloroform (20ml.) and this solution was washed with bicarbonate solution, dried (Na_2SO_4) and evaporated under diminished pressure. The residual light brown oil solidified. The enol acetate of γ-phenyl tetronic acid thus obtained crystallised from light petroleum (b.p.60-80°) as needles m.p.79°, undepressed on admixture with a specimen prepared by the previous method.

Acetonyl isopropylidene-bis-γ-phenyl tetronic acid. (cf. L. Wolff and W. Schlimpff, Ann.,1901,315,151).- γ-Phenyl tetronic acid was heated under reflux in acetone (30ml.) containing a trace of piperidine, for 30 minutes. The mixture was left to stand for 2.5 hours when a further quantity of acetone 30ml.) was added and the mixture was again heated under reflux for an hour. Excess acetone was evaporated and the gum

remaining was solidified by treatment with ether. The solid was ground with ethyl acetate and the colourless solid residue was collected. When crystallised several times from ethanol, acetonylisopropylidene-bis-γ-phenyl tetronic acid had m.p.177°. (Found C,72.1%; H,5.75%. $C_{26}H_{24}O_6$ requires C,72.2%; H,5.6%.).

In ethanolic solution the compound gave a red colour with ferric chloride solution and in water it showed slight acidity.

Reaction of γ-phenyl tetronic acid with alkali.-

γ-Phenyl tetronic acid (5g.) was boiled in sodium hydroxide solution (2g. in 20ml. water) under reflux for 2 hours. When cool the solution was acidified with strong sulphuric acid and the precipitate was collected. The precipitate was dissolved in chloroform, the organic layer was dried (Na_2SO_4) and chloroform was evaporated under diminished pressure. γ-Phenyl tetronic acid (4g.) was recovered as a cream coloured solid, which crystallised from water and had m.p.127°.

Attempted C-acylation of γ-phenyl tetronic acid.-

(i) γ-Phenyl tetronic acid (0.9g.) was heated under reflux with acetic anhydride (15ml.) and pyridine (3ml.). The mixture rapidly turned brown and when poured into water a dark brown intractable tar was obtained.

(ii) γ-Phenyl tetronic acid (1.6g.) and anhydrous sodium acetate (0.2g.) were dissolved in acetic anhydride (10ml.) and the solution was heated on a water bath for thirty minutes. When cool, water (30ml.) was added and the mixture was left overnight at room temperature. The solution was extracted with chloroform the extract dried (Na_2SO_4) and the solvent was evaporated under diminished pressure. A solid remained and this was found to be unchanged γ-phenyl tetronic acid.

Attempted C-alkylation of γ-phenyl tetronic acid.- γ-Phenyl tetronic acid (5g.) was mixed with tert-butanol (3.5ml.) and syrupy phosphoric acid (20ml., 98%, S.G.1.85) and the mixture was heated on a water bath for 2 hours. After it had cooled the mixture was treated with warm water and the solution was extracted several times with ether. The ether was dried (Na_2SO_4) and evaporated under diminished pressure. A solid was obtained (3.8g.) and this crystallised from water and had m.p.126°. It was found to be unchanged γ-phenyl tetronic acid. A colourless liquid was also obtained which had n_D^{16}1.4411. It was very unreactive being neutral and insoluble in water. It gave no colour with ferric chloride solution and possessed no ketonic function.

Ethyl 2'-tetrahydropyranyloxyacetate.- Method I. One drop of concentrated hydrochloric acid was added to a mixture of redistilled 2:3-dihydropyran (29.5g.) and ethyl glycollate (19.5g.). The temperature rose rapidly but was maintained below 40° by cooling the reaction vessel in running water. When the mixture had stood for 3 hours a few pellets of potassium hydroxide were added to remove acid. The liquid was distilled under diminished pressure, excess dihydropyran came over first and ethyl 2'-tetrahydropyranyloxyacetate (30g. 80%) distilled at 73.5%.4mm. as a colourless liquid n_D^{16}1.4440. (Found: C,57;4%. H,8:45%; $C_9H_{16}O_4$ requires C,57.4%; H,8.50%).

Method II. To a mixture of redistilled 2:3-dihydropyran (17g.) and ethyl glycollate (16g.) was added an acid ion exchange resin ('Amberlite' IR 120 H 0.5g.[Dried]). The temperature rose slowly from 22° to 26°. The mixture was left 20 hours at room temperature, filtered and distilled as before. The yield was 12.2g. (70%).

The amide was prepared by standing the ester in excess 0.880 ammonia solution overnight. It crystallised after removal of solvent under diminished pressure. It was recrystallised from benzene, forming colourless prisms m.p.66.5°. (Found: C,53.0%; H,8.20%; N,8.65%. $C_7H_{13}O_3N$ requires C,52.8%; H,8.20%; N,8.80%).

Hydrolysis of ethyl tetrahydropyranyloxyacetate.- By hydrolysis with sodium hydroxide solution (20ml. of c.1N), followed by estimation of excess alkali, the equivalent of the ester was found to be 187 ($C_9H_{16}O_4$ requires equivalent 188).

2'-Tetrahydropyranyloxyacetic acid.- Ethyl tetrahydropyranyloxyacetate (20g.) was hydrolysed by standing at room temperature with sodium hydroxide solution (30ml.4.21N) until the solution became homogeneous (2.5 days). Unhydrolysed material was extracted with ether. Ether (50ml.) was then added to the residual aqueous solution and the vessel was cooled in ice whilst the theoretical quantity of hydrochloric acid (1N) was run in. After separation and two further extractions the ether layer was dried (Na_2SO_4). Ether was removed under diminished pressure at room temperature, the last traces of water were removed by azeotropic distillation with chloroform. A viscous colourless liquid remained which was water soluble, effervesced with bicarbonate, was acid to methyl red, and had n_D^{17} 1.4444. A determination of the equivalent by titration with sodium hydroxide gave a value of 181. $C_7H_{12}O_4$ requires equivalent of 160.

On heating the acid evolved gas and turned brown, and distillation, even at very low pressure, was not possible. With thionyl chloride, hydrogen chloride was

evolved and on removing excess thionyl chloride by distillation under diminished pressure at room temperature a brownish liquid was obtained which resinified on warming.

The Claisen condensation of ethyl tetrahydropyranyloxy-acetate.- The ester (20g.) was dissolved in its own volume of dry ether and added gradually to sodium wire (2.70g.) under dry ether (100ml.) whilst a stream of dry nitrogen was passed through the liquid. The reaction was left at room temperature for 24 hours, effervescence occurred and the sodium slowly reacted to give an insoluble yellow sodio compound. When the reaction had been brought to completion by heating under reflux on a water bath for one hour the mixture was brown in colour.

A little ethanol was added to destroy excess sodium. Water was added to decompose the sodio compound and the mixture was cooled to 0°C. and made acid with tartaric acid (10g. in 50ml. water + 50ml. ice). The product was extracted with ether and the ethereal solution was dried (Na_2SO_4). The solvent was then removed under diminished pressure without heating.

The crude brownish-red oil remaining (24g.) could not be distilled under ordinary conditions, but it was found possible to distil the liquid in a short path distillation apparatus and several fractions were obtained.

(Boiling points refer to the temperature recorded by the thermometer placed in glass socket passing through the liquid, but as good thermal contact was not possible, these provide only an indication as the term 'boiling point' has little significance in this method of purification).

The liquid was distilled in portions of 20g. After 4 hours evacuation of the vessel, heating was commenced and the temperature increased slowly to 120° over 10 hours. After distillation about 4g. dark brown material remained in the vessel.

Fractions obtained.-

1). B.P. 75- 98°/0.05mm. $\underline{n}_D^{13.5}$ 1.4620 (2.47g.)

2). B.P. 98-113°/0.05mm. $\underline{n}_D^{13.5}$ 1.4674 (1.70g.)

3). B.P. 113-122°/0.05mm. $\underline{n}_D^{13.5}$ 1.4730 (1.70g.)

(In other experiments a more volatile fraction which was unchanged starting material was collected at temperatures from 60-70° but this must have volatilised completely in the experiment recorded above).

Fraction 1) in ethanolic solution rapidly gave a red brown colour with ferric chloride. It was probably a mixture of some unchanged starting material with Fraction 2).

Fraction 2) in ethanol gave rapidly a similar colour with ferric chloride. It was a yellowish liquid which on standing for some days turned brown. It gave easily a purple colour on the addition of saturated aqueous o-dinitrobenzene followed by a few drops of alkali,

indicative of an ene-diol system (W. R. Fearon and E. Kawerau, Biochem.J.,1943,37,326).

Fraction 3) was ethyl 1:3-bis-2'-tetrahydropyranyloxy-2-keto butyrate, a yellow viscous oil, which in ethanolic solution slowly gave a purple lilac colour with ferric chloride.

(Found: C,57.8%; H,8.0%. $C_{16}H_{26}O_7$ requires C,58.2%; H,7.9%). It had light absorption in ethanol: maximum at 2620A. ($\varepsilon_{max.}$ 700) and this maximum was shifted to longer wavelengths by addition of sodium ethoxide.

Reaction of ethyl 1:3-bis-2'-tetrahydropyranyloxy-2-ketobutyrate with phenylhydrazine.- The ester (0.5g.) and phenylhydrazine (0.5g.) were heated on a water bath during 1 hour. The colour changed to red on mixing. The gum did not solidify on treatment with petrol, but after dissolving in a mixture of benzene and light petroleum (b.p.60-80°) and absorbing on alumina column an orange band separated which was eluted with the solvent to give an orange-coloured solution which deposited crystals on evaporation. Recrystallisation from ethanol gave orange prisms m.p.123° (Found: C,66.7%; H,5.80%; N,14.4%. $C_{21}H_{22}O_3N_4$ requires C,66.7%; H,5.80%; N,14.8%). The formulation of this compound has been discussed in the text.

Hydrolysis of ethyl 1:3-bis+2'-tetrahydropyranyloxy-2-ketobutyrate.

I) Under acid conditions.- The ester (2.85g.) was hydrolysed by shaking in the cold with 0.2N sulphuric acid (10ml.) under an inert atmosphere for 3 days. Sulphuric acid was removed by addition of the theoretical amount of barium hydroxide solution (0.1N). The liquid remained acid (pH 3-4). Barium sulphate was filtered off using Whatman No.5 filter paper and water was removed by freeze drying, when a yellow oil remained. A drop of the aqueous solution with a few drops of aqueous sodium bicarbonate gave a deep blue colour with ferric chloride solution.

The yellow oil would not reduce aqueous 2:6-dichlorophenol-indophenol blue, but merely gave a red colour indicative of an acid reaction, however after the addition of a few drops of sodium bicarbonate solution, restoration of the blue colour was followed by rapid reduction of the indicator to the colourless form.

The oil was examined by paper chromatography using n-butanol/glacial acetic acid/water (40:10:50, v/v). A crystal of potassium cyanide was added to the solvent to prevent oxidation catalysed by copper ions. Ascorbic acid was used as a reference compound.

After 20 hours the paper was sprayed with 2:6 dichlorophenol indophenol blue in water/ethanol (50:50) and a very small white spot on a red background (R_F 0.67)

corresponding to hydroxytetronic acid was obtained. On spraying the paper with bicarbonate solution the colour of the background turned blue and a long white streak developed near the solvent front showing that the main constituent of the oil was not hydroxytetronic acid.

The yellow oil was further hydrolysed by standing in the cold with concentrated hydrochloric acid (2ml. with 2ml. water) for 20 hours. Solvent was removed by standing the liquid overnight in a vacuum desiccator over potassium hydroxide pellets.

Hydroxytetronic acid crystallised as needles, which turned brown on standing for several hours. The material when collected was gum-like and attempts to recrystallise it from dry solvents failed.

Examination by paper chromatography, as previously described, produced a large spot corresponding to hydroxytetronic acid, which reduced 2:6-dichlorophenol indophenol blue without bicarbonate treatment. When sprayed with bicarbonate solution only a very small spot appeared near the solvent front, R_F values:-

Measured values:	(L. Mapson and S. M. Partridge) Nature, 1949, 164, 479.
Ascorbic acid 0.39	0.37
Unknown 0.66	0.63 Hydroxytetronic acid
R_A = 0.17	0.17

[where $R_A = R_F$ (ascorbic acid)/R_F (hydroxytetronic acid]

From these measurements of R_F values it was concluded that the material examined was hydroxytetronic acid.

Hydroxytetronic acid bis-phenylhydrazone:- Hydroxytetronic acid (0.5g. gum from hydrolysis) was left to stand at room temperature with phenylhydrazine (1.5g.) and a drop of glacial acetic acid, for 48 hours. The red solid (0.7g.) was filtered off and recrystallised from ethanol. On the Kofler block it had m.p. 168° and 215° (d.). F. Micheel and F. Jung, (Ber., 1934, 67, 1660) report m.p. 180° (labile form) changing after melting into the stable form m.p. 238°. (Found: C, 65.25%; H, 5.05%; N, 19.1%. $C_{16}H_{14}N_4O_2$ requires C, 65.30%; H, 4.75%; N, 19.05%).

II) Under alkaline conditions:- The ester (4.5g.) was left to stand in the cold 24 hours with aqueous methanolic sodium hydroxide solution (1.0g. in 100ml. methanol and 10ml. water). Water (100ml.) was added and the solution was extracted several times with ether. The extract was dried (Na_2SO_4) and solvent was removed in the cold under diminished pressure when a yellow oil A (1g.) was obtained. The aqueous solution was acidified with a slight excess of aqueous tartaric acid and extracted with ether. The extract was dried (Na_2SO_4), solvent was removed in the cold under diminished pressure and a yellow oil B was obtained.

Fraction A was purified by short path distillation at 85-90° (bath temperature)/0.01mm. $n_D^{17.5}$ 1.4748. It was 1:3-bis-2'-tetrahydropyranyloxyacetone (Found: C,60.60%; H,8.50%. $C_{13}H_{22}O_5$ requires: C,60.45%; H,8.55%). Fraction B in ethanol gave no colour with ferric chloride. It was probably also 1:3-bis-2'-tetrahydropyranyloxyacetone arising by decarboxylation of an intermediate substituted acetoacetic acid.

Reaction of 1:3-bis-2'-tetrahydropyranyloxyacetone with p-nitrophenylhydrazine.- The compound (0.25g.) in ethanol (25ml.) was heated to boiling with p-nitrophenylhydrazine (0.5g.), when concentrated hydrochloric acid (1ml.) was added. The mixture was boiled for 2 minutes and when cool the dark red precipitate was collected. Recrystallised from nitrobenzene it had m.p.280°(d.) on the Kofler block. H. Dakin and H. Dudley, (J.Biol.Chem.,1913,15,137 report m.p.310° for p-nitrophenyl osazone of 1:3-dihydroxyacetone). With sodium hydroxide in ethanol the compound gave a blue colour which turned red on standing (Given also by authentic osazone of 1:3-dihydroxyacetone-. H.P.den Otter, Rec.Trav.chim.1937,56,482).

Acid Hydrolysis of 1:3-bis-2'-tetrahydropyranyloxyacetone.- The adduct (5mg.) was left to stand 18 hours at room temperature with sulphuric acid (2ml. of 0.1N). To a

little of the solution was added several drops of saturated o-dinitrobenzene followed by a few drops of sodium hydroxide solution. The rapid developement of a purple colour showed the presence of an ene-diol system (W. R. Fearon and E. Kawerau, loc.cit.).

The hydrolysate was examined by paper chromatography on Whatman No.1 paper.

i) n-butanol/glacial acetic acid/water (20:5:25.v./v.) was used as a solvent system and the paper was sprayed with ammoniacal silver nitrate, after 7 hours. Commercial dihydroxyacetone was used as a reference substance and gave 2 spots the most intense of which corresponded to a spot from the hydrolysate (R_F 0.5).

ii) This was repeated and after 18 hours the paper was dried and passed through a solution made by diluting saturated aqueous silver nitrate solution (0.1ml.) to 20ml. with acetone and adding water dropwise to redissolve precipitated silver nitrate. When dry the paper was sprayed with a 0.5N aqueous ethanolic solution of sodium hydroxide. The paper was then immersed in 6N ammonium hydroxide solution for a few minutes and washed with running water for an hour. (W. E. Trevelyan, D. P. Procter and J. S. Harris, Nature,1950,166,444). Black spots were produced against a white background.

Commercial dihydroxy-acetone gave 2 spots (R_F0.45 and R_F 0.325). The hydrolysate gave 2 spots, having the

same R_F values. The first of these spots was most intense. In addition streaking from the solvent front to the spot was observed.

iii) Under the same conditions, glyceraldehyde, commercial dihydroxyacetone and the hydrolysate were examined. Glyceraldehyde showed a pear shaped streak which had run for the same distance as the most intense spot (R_F 0.45) shown by the other two compounds.

iv) The same results were obtained when an aniline oxalate spray was used.

v) Examination was repeated using n-butanol/pyridine/water (3:2:1.5,v./v.) as a solvent system and spraying first with sodium borate solution then with phenol red indicator (D. J. Hockenhull, Nature,1953,171,982). Commercial dihydroxyacetone gave a spot (R_G:1.78) and a fainter spot (R_G:0.86). The hydrolysate gave a spot (R_G:1.78) (Hockenhull gives R_G:1.84 for dihydroxyacetone on Whatman No.4 paper) but also produced spots of lower R_G values, the most intense having R_G:0.27.

From the above experiments indications of identity of the hydrolysate with 1:3-dihydroxyacetone were obtained but the commercial specimen of the latter did not show homogeneity, so that proper comparison of the behaviour of the two, when examined by paper chromatography, could not be made. However, the principal spot obtained from

the hydrolysate when the solvent systems described were used for examination, coincided with the principal spot from commercial 1:3-dihydroxyacetone.

Synthesis of the lactone of β-hydroxy-β-(1-hydroxycyclohexyl) acrylic acid (cf. E. R. H. Jones and M. C. Whiting, J.Chem.Soc.,1949,1423),

i) β-N-piperidino-β-(1-hydroxycyclohexyl) acrylic acid lactone.- Redistilled piperidine (3g.) was added to a solution of the ethyl ester of β-(1-hydroxycyclohexyl)-propiolic acid (4.1g.) in dry ether (25ml.) and the solution was left to stand for 48 hours at room temperature. A further quantity of piperidine (3g.) was added and ether was distilled off slowly. The residue was heated for 2 hours on a steam bath. When cool, solidification was effected by treatment with light petroleum (b.p.60-80°). The yield of β-N-piperidino-β-(1-hydroxycyclohexyl) acrylic acid lactone was (4.55g.,83%). It crystallised from light petroleum (b.p.60-80°) as colourless needles which had m.p.104.5° (Found C,71.0%; H,8.8%; N,5.55%. $C_{14}H_{21}O_2N$ requires C,71.5%; H,8.9%; N,5.95%).

ii) Hydrolysis of β-N-piperidino-β-(1-hydroxycyclohexyl) acrylic acid lactone.- The piperidino compound (3g.) was treated with concentrated hydrochloric acid (10ml.). It dissolved on warming to give a pink solution, which was heated on a steam bath for 40 minutes. Solid was precipitated after 5 minutes. When the liquid was cold, the white crystalline solid was collected and sucked dry at the pump. The yield of the lactone of

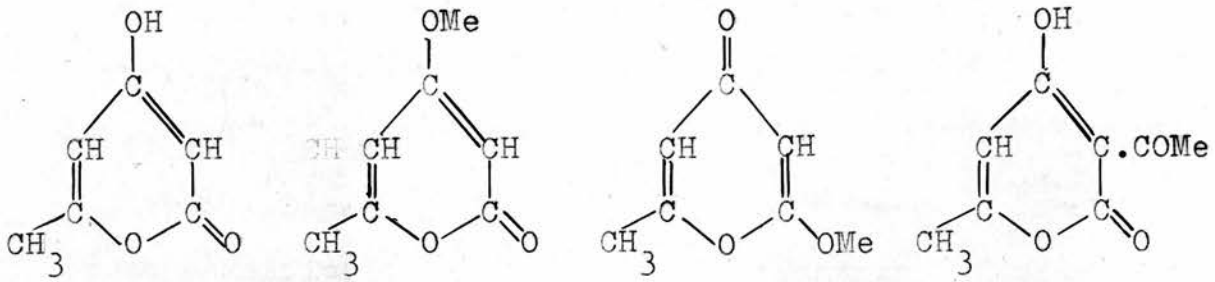
β-hydroxy-β-(1-hydroxycyclohexyl) acrylic acid was 2g. (92%). It crystallised from ethyl acetate as colourless prisms m.p.197.5°. E. R. H. Jones and M. C. Whiting (J.Chem.Soc.,1949,1419) gave m.p.198°.

Lactone of β-methoxy-β-(1-hydroxycyclohexyl) acrylic acid.- (E. R. H. Jones and M. C. Whiting, J.Chem.Soc.,1949,1419).- The lactone of β-hydroxy-β-(1-hydroxycyclohexyl) acrylic acid (0.5g.), methyl iodide (2g.) and 4N sodium hydroxide solution (0.7ml.) were added to methanol (3ml.). After 5 days the neutral fraction was isolated by ether extraction of the solution [to which water (5ml.) had been added] followed by washing the extract with bicarbonate solution. When dried (Na_2SO_4) the extract was evaporated and the residue solidified. The solid was extracted with boiling light petroleum (b.p.40-60°), on cooling the solution the ether crystallised m.p.102-3°. Recrystallised from this solvent it formed colourless needles m.p.104°. E. R. H. Jones and M. C. Whiting (loc.cit.) give m.p.104°.

U. V. LIGHT ABSORPTION STUDIES.

PREPARATION OF COMPOUNDS FOR U.V. LIGHT ABSORPTION STUDIES.

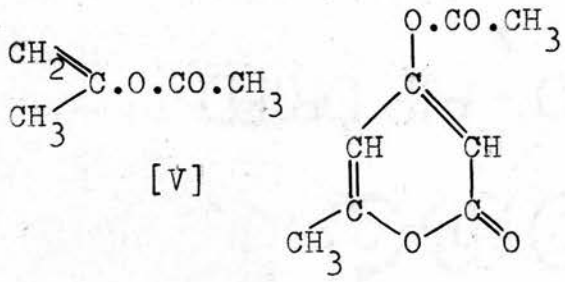
When the U.V. light absorption properties of some tetronic acids had been studied, it was desirable to prepare some derivatives of β-keto compounds for purposes of comparison. The first of these compounds was 6-methyl pyronone [I] (J. N. Collie, J.Chem.Soc., 1891,609; 1907,787) which was of interest because of the inclusion of the enolised β-keto system in a 6-membered ring. The compound is fully enolised (F. Arndt and S. Avan, Ber.,1951,84,343) and on methylation gives ether which was formulated by F. Sproxton (J.Chem.Soc., 1906,1186) as [II], and ∝-pyrone derivative. However, F. Arndt (loc.cit.) considers that as this compound is water soluble and forms a hydrochloride it should be formulated as a γ-pyrone derivative [III] on the basis of his demonstration in a previous paper (F. Arndt, L. Loewe, R. Un and E. Ayça, Ber., 1951,84,319) that γ-pyrone derivatives are distinctly basic whereas those of ∝-pyrone are not. Therefore,not only was this compound of interest as a methyl ether but also in its relationship to the structure of the parent compound. Pyronone was prepared by the method of Collie (loc.cit.) from dehydracetic acid [IV] by treatment with strong sulphuric acid, when a $-CO.CH_3$ group is eliminated.



[I] [II] [III] [IV]

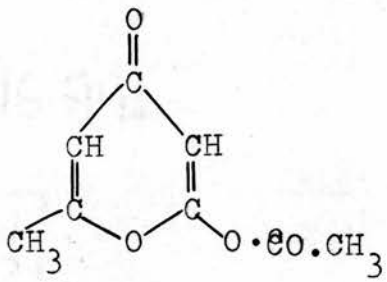
The methyl ether of 6-methyl pyronone was prepared by three different routes:- (i) by treatment of the silver salt with methyl iodide (Sproxton, loc. cit.); (ii) by action of diazomethane on 6-methyl pyronone (F. Arndt and S. Avan, loc.cit); (iii) by the action of methanol saturated with hydrogen chloride on 6-methyl pyronone. In each case the same product was isolated so that there is no question involved of O-methylation at alternative sites. For comparison an enol acetate was prepared from pyronone by the action of iso-propenyl acetate [V] on 6-methyl pyronone. After the reaction had been initiated by acid in catalytic quantity, acetone was distilled off as the reaction proceeded and the acetate was obtained by extraction of the residue with light petroleum. The acetate [VIa] or [VIb] was obtained and its relevance to the structural problem outlined will be discussed in a later section, but its properties led to the conclusion that [VIa] is probably the more

correct formula. The method of enol acetylation by the use of isopropenyl acetate has been found of wide application (H. J. Hagemeyer and D. C. Hull, Ind.Eng.Chem., 1949,41,2920) and provides an elegant method for the preparation of many enol acetates otherwise obtainable only with great difficulty.



[V]

[VIa]



[VIb]

For spectroscopic studies enol acetates were also prepared from ethyl acetoacetate, 5:5-dimethylcyclohexane-1:3-dione, and phenyl tetronic acid by the above method and in each case the reaction proceeded smoothly to give the desired product.

6-Methyl Pyronone.- (J. N. Collie, J.Chem.Soc.,1891, 607). A solution of dehydracetic acid (50g.) in 90% (v./v.) sulphuric acid (150g.) was warmed in an oil bath to 130°. Heating was continued until a little of the yellow solution no longer gave crystals when dropped into cold water. The solution was poured into cold water and set aside to cool. The crystals were collected and sucked dry at the pump. The yield was 21g. (51%). The compound crystallised from dioxan as straw coloured needles and had m.p.186°. J. N. Collie (loc.cit.) gives m.p.188-9°. Light absorption in methanol showed $\lambda_{max.}$ 2820-2830A. ($\varepsilon_{max.}$ 7,100) and $\lambda_{min.}$ 2410A. ($\varepsilon_{min.}$ 1040). J. A. Berson (J.Am.Chem.Soc.,1952,74,5172) gives $\lambda_{max.}$ 2830A. ($\varepsilon_{max.}$ 8,920).

Methyl ether of 6-methyl pyronone.- (i) (F. Sproxton, J.Chem.Soc.,1906,1186). A concentrated aqueous solution of 6-methyl pyronone (10g.) was neutralised with concentrated ammonia solution and to the solution of the ammonium salt thus formed, excess silver nitrate solution was added. The precipitate of the silver salt (13.8g.74.6%) was collected and dried in a desiccator. The dried silver salt was heated under reflux for one hour in dry methanol (50ml.) and methyl iodide (35ml. purified by heating 20 mins. with silver oxide under reflux then distilled). Silver iodide was removed by

filtration and the solvent was removed by distillation under diminished pressure. The residue was extracted with ether and the solution was evaporated under diminished pressure. The yield was 1.8g. (30%) of pale brown solid m.p.73°. When recrystallised from light petroleum (b.p.60-80°) it had m.p.80°. Purification was difficult as the material became brown and sticky after treatment with light petroleum. Further recrystallisation from light petroleum (b.p.60-80°) gave colourless plates m.p.84-5° F. Sproxton (loc.cit.) gives m.p.81°. Light absorption in methanolic solution showed $\lambda_{max.}$ 2790A. ($\varepsilon_{max.}$ 6,350) and $\lambda_{min.}$ 2390-2410A. ($\varepsilon_{min.}$ 1,050). J. A. Berson (loc.cit.) gives $\lambda_{max.}$ 2800A. ($\varepsilon_{max.}$ 8,810).

(ii) (F. Arndt and S. Avan, Ber.,1951,84,343) 6-Methyl Pyronone (3g.) was treated with excess ethereal diazomethane and vigorous evolution of nitrogen occurred. Some brown gum-like substance remained undissolved, even when the reaction mixture had been left to stand overnight. The ether was removed under diminished pressure and the brown residue was extracted with light petroleum (b.p.60-80°). The same difficulties were encountered in purification as in the previous method. Recrystallised twice from light petroleum (b.p.60-80°) the compound had m.p.83°. Its identity with the compound prepared by method (i) was shown by u.v. light absorption measurements.

(iii) 6-Methyl pyronone (10g.) was dissolved in dry methanol (100ml.) previously saturated with hydrogen chloride. The reaction was left to stand at room temperature for 26 hours and then the solution was poured on to crushed ice. The mixture was extracted with benzene (2 portions of 100ml.) and the extract was washed, once with a saturated solution of sodium bicarbonate (50ml.), once with sulphuric acid (30ml. dilute acid with 20ml. water), and finally with water (2 portions of 50ml.). Solvent was removed from the yellow solution by distillation under diminished pressure at a bath temperature of not more than 35°. A yellow solid was obtained and the yellow coloured material was easily removed by crystallisation from light petroleum (b.p.60-80°) in which it was much more soluble than the methyl ether of pyronone. The impure material (3.2g.,28%) had m.p.80° and was much easier to purify than the material obtained by the previous methods. Recrystallised from light petroleum the ether had m.p.87°. Mixed m.p. with pyronone methyl ether prepared by method (i) 85°. U.V. light absorption properties were identical with those of the compound prepared by method (i).

6-Methyl pyronone enol acetate.- One drop of a 10% solution of 2:5-dichlorobenzoic acid in methanol was added to a mixture of 6-methyl pyronone (2.45g.) and

isopropenyl acetate (10ml.) and the mixture was warmed on a water bath under reflux until all the solid dissolved. The mixture was left to stand overnight. The solution was heated on a water bath under reflux for 20 minutes and then acetone and excess isopropenyl acetate were removed by distillation under diminished pressure. The brown syrup which remained, solidified and was dissolved in ether (150ml.). The ethereal solution was shaken with sodium bicarbonate solution, dried (Na_2SO_4), and evaporated under diminished pressure. The brown oil obtained solidified on scratching and seeding with solid previously obtained. Recrystallised from light petroleum (b.p.60-80°) it had m.p.41°.
The enol acetate of 6-methyl pyronone crystallised from light petroleum (b.p.40-60°) as long colourless needles m.p.45° (Found: C,57.2%; H,4.9%. $C_8H_8O_4$ requires C,57.15%; H,4.8%). Light absorption in methanolic solution showed $\lambda_{max.}$ 2890-2900A. ($\varepsilon_{max.}$ 5,930) and $\lambda_{min.}$ 2430A. ($\varepsilon_{min.}$ 990).

2:6-Dimethyl-γ-pyrone.- (J. N. Collie, J.Chem.Soc.1891,617) Dehydracetic acid (10g.) was boiled under reflux for one hour with concentrated hydrochloric acid (75ml.). The volume of the green solution was reduced by evaporation under diminished pressure. Sodium hydroxide solution was added to bring the solution to pH 9 and then

the solution was extracted with ether. The ethereal solution was dried (Na_2SO_4). When the ether had been evaporated, crystals of 2:6-dimethyl-γ-pyrone (3.3g.,50%) remained and had m.p.131°. The compound crystallised from ethanol as white needles m.p.132°. J. N. Collie (loc.cit.) gives m.p.132°. Light absorption in ethanol showed $\lambda_{max.}$ 2450A. ($\varepsilon_{max.}$ 16,100) and $\lambda_{min.}$ 2230-2240A. ($\varepsilon_{min.}$ 7,810).

5:5-Dimethyl-cyclohexane-1:3-dione enol acetate.- Isopropenyl acetate (20ml.) was added to 5:5-dimethyl-cyclohexane-1:3-dione (7g.) in dioxan (20ml.) with 1 drop of concentrated sulphuric acid as a catalyst. When the mixture had been warmed for 20 minutes on a water bath, acetone was distilled and the liquid was mixed with ether (20ml.). The solution was washed with saturated sodium bicarbonate solution and dried (Na_2SO_4). Ether, dioxan and excess isopropenyl acetate were distilled under diminished pressure on a water bath. The residual brown liquid was distilled under diminished pressure and 5:5-dimethyl-cyclohexane-1:3-dione enol (5g.,55%) was obtained as a colourless liquid b.p. 80°/0.1mm. $n_D^{18.5}$ 1.4789 (Found: C,65.4%; H,7.5%. $C_{10}H_{14}O_3$ requires C,65.9%; H,7.75%).

Ethyl β-acetoxycrotonate.- (H.J.Hagemeyer and D. C. Hull, Ind.Eng.Chem.,1949,41,2920). Acetoacetic

ester (50g.) was mixed with isopropenyl acetate (40g.) and 8 drops of a 10% methanolic solution of 2:5-dichlorobenzoic acid was added to initiate reaction. The mixture was heated on a water bath for one hour under reflux and then left overnight at room temperature. The mixture was heated on a water bath until acetone (11.5ml.) distilled over and heating was continued for a further 5 hours. The mixture was fractionated by distillation under diminished pressure through a short column. The following fractions were obtained

1) B.p.53-58°/0.3mm. $n_D^{9.5}$ 1.4362 (10g.)

2) B.p.61-64°/0.3mm. $n_D^{9.5}$ 1.4438 (17.0g.)

3) B.p.65-66°/0.3mm. $n_D^{9.0}$ 1.4476 (27.5g.,42%)

H. J. Hagemeyer and D. C. Hull (loc.cit.) give b.p.94°/10mm. and n_D^{20} 1.4420 for ethyl β-acetoxycrotonate and its isomer.

ULTRA-VIOLET LIGHT ABSORPTION STUDIES

The ultra-violet light absorption of tetronic acid ∝-ethyl tetronic acid, ɣ-phenyl tetronic acid and the lactone of ∝-hydroxy-β-(1-hydroxycyclohexyl) acrylic acid have been studied in polar solvents and the absorption curves are shown. The observations of R. W. Herbert and E. L. Hirst (Biochem.J.,1935,39,1881) and of E. R. H. Jones and M. C. Whiting (J.Chem.Soc., 1949,1423) have been confirmed and extended. The acids in ethanolic solution show a singly banded spectrum in the region of 2250A. which, on dilution of the absorbing solution,is displaced towards the red end of the spectrum. This displacement is due to ionisation of the acid and when the acid is completely ionised the absorption band is shifted to the region of 2500A. (cf.E. R. Blout, V. W. Eager and D. C. Silverman, J.Am.Chem.Soc.,1946,68,566). The presence of an ∝-alkyl group, as in ∝-ethyl tetronic acid, produces a displacement to-wards the red of ca.80A. A solution of the acid in ethanol with a trace of hydrochloric acid absorbs at 2330A. and in dilute ethanolic solution when the acid is completely ionised the absorption band is at 2580A. This observation might be expected from the predictions of R. B. Woodward (J.Am.Chem.Soc.,1941,63, 1123; 1942,64,76) concerning the effect of alkyl

substituents on the absorption bands of simple $\alpha\beta$ unsaturated ketones, in which an α-alkyl substituent would produce bathochromic effect of 80-90A. The parallel between the behaviour of tetronic acids and mono-enolised β-diketones in which intra-molecular hydrogen bonding is prevented on steric grounds has been further extended. A series of measurements on the absorption spectra of the acids in aqueous or aqueous ethanolic solution at various pH values was made. From these measurements the dissociation constants of the acids were calculated and compared with those obtained by potentiometric titration.

The dissociation constants can be calculated from the extinction coefficients by the following method (L. A. Flexser, L. P. Hammett and A. Dingwall, J.Am. Chem.Soc.,1935,57,2103; cf. also W. Stenström and N. Goldsmith, J.Phys.Chem.,1926,30,1683). If a solute exists in two forms say HA and A^- then the total concentration C is given by equation [I].

C_{A^-} and C_{HA} are the concentrations of the ion and the undissociated acid, respectively and the dissociation constant of the acid is given by the equation:

$$pK_a = pH - \log \frac{C_{A^-}}{C_{HA}}$$

$\frac{C_{A^-}}{C_{HA}}$ can be determined spectroscopically.

$$C = C_{A^-} + C_{HA} \qquad [1]$$

Beer's law gives: $\varepsilon = \frac{D}{Cl}$ [2]

If each substance absorbs independently:

$$D = (\varepsilon_{A^-} C_{A^-} + \varepsilon_{HA} C_{HA}) \qquad [3]$$

from [1], [2] and [3]

$$\frac{C_{HA}}{C_{A^-}} = \frac{\varepsilon - \varepsilon_{A^-}}{\varepsilon_{HA} - \varepsilon}$$

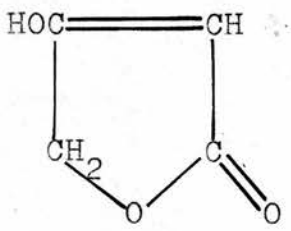
For an acid ε_{HA} is found by increasing the acidity to a point where A^- is vanishingly small and ε_{A^-} is similarly determined by making the solution basic sufficiently to ionise the acid completely.

The method has been slightly modified by J. C. Gage, (J.Chem.Soc.,1949,221). ε_{A^-} and ε_{HA} are measured at the same wavelength. The precision of the method depends on the magnitude of the difference between ε_{HA} and ε_{A^-} if the addition of a proton only produces a small change in the spectrum then the method may involve a large error. This error can be minimised by replacing the optical density values in the above equation by the difference in density of the spectrum at 2 values selected

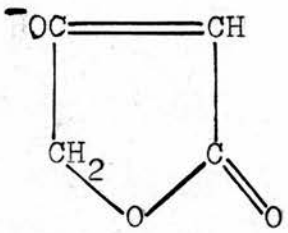
so that the change in this difference in passing from one form to the other is a maximum. The values obtained by this method were, for tetronic acid in 80% aqueous ethanol: pKa 4.3 (average) (Potentiometric determination gave pK_a 4.4); and for γ-phenyl tetronic acid in water: pK_a 3.0 (average) (Potentiometric determination gave pK_a 3.75). The figure for γ-phenyl tetronic acid is somewhat lower than that obtained by potentiometric titration, but with the enolic form of this compound it is difficult to obtain a clearly defined maximum in the 2100-2300A. region of the spectrum (v. graphs of U.V. absorption spectra). The result is sufficient to indicate that a γ-substituent has little effect on the acidic strength (cf. tetronic acid in water, pK_a 3.76 [W. D. Kumler, J.Am.Chem.Soc.,1938,60,859]).

The curves show a unique isosbestic point and the importance of this has been pointed out by L. A. Flexser, L. P. Hammett and A. Dingwall (loc.cit.) as an indication that a solute exists in only two forms. These two forms have equal extinction coefficients at some wavelength so that if the absorption curves of the two intersect for one solution they must intersect for all of the solutions as these contain only various mixtures of the two individuals. Conversely, if two curves intersect at a point which is not common to all the other curves then it must be true that more than

two forms are present. In the present case the two species involved in light absorption must be the ion [II] and the undissociated enol [I].



[I]



[II]

That one of the species is the enolic form [I] is shown by the similarity in its absorption intensity and maximum to that of the methyl ether. (E. R. H. Jones and M. C. Whiting, loc.cit.). For example in the case of γ-phenyl tetronic acid where the undissociated enol has $\lambda_{max.}$ 2200-2250A. (log.ε 4.3) in water, R. A. Raphael (J.Chem.Soc.,1949,118) found that the methyl ether had $\lambda_{max.}$ 2200A. (log.ε 4.22.) in ethanol.

The spectrum of $\alpha\alpha$-dimethyl-β-keto-γ-butyrolactone in ethanol is entirely different from that of the tetronic acids, showing a very low intensity of absorption and possessing no maximum in the region 2200-2350A. Therefore the characteristic ultra-violet spectra of the tetronic acids must be regarded as due to the presence of an enolisable β-ketonic group.

∝-Acetyl and ∝-carbethoxy tetronic acids in aqueous solution show a doubly banded absorption spectrum, which is typical of enolised β-triketones (A. J. Birch and A. R. Todd, J.Chem.Soc.,1952,3102). The bands appear at 2650A. and 2300A. in the case of ∝-acetyl-γ-phenyl tetronic acid in aqueous solution and bands are observed in the same regions in the case of many other ∝-acetyl-γ-substituted tetronic acids [R. W. Herbert and E. L. Hirst (loc.cit.) and R. N. Lacey (J.Chem.Soc.,1954,832)]. A further parallel can be drawn with β-triketonic compounds, as 2-acetyl-cyclohexane-1:3-dione shows a similar spectrum with bands at 2350A. ($\varepsilon_{max.}$ 14,700) and 2750A. ($\varepsilon_{max.}$ 11,600) (H. Smith, J.Chem.Soc.,1953,803).

The bands shown by ∝-acetyl-γ-phenyl tetronic acid and ∝-carbethoxy-γ-phenyl tetronic acid in aqueous solution were not displaced when the pH of the medium was altered. In ethanolic solution bands in the same position were observed and there was no change in their position when sodium ethoxide was added to the solution. However, when a little hydrochloric acid was added to the ethanolic solution the maximum was displaced and ∝-acetyl-γ-phenyl tetronic acid showed only a singly banded spectrum with a maximum at 2700A. ∝-Carbethoxy-γ-phenyl tetronic acid also showed a singly banded spectrum in this medium with a maximum at 2370A. compared with 2490A. in aqueous solution or in neutral ethanolic solution.

The enol acetates of some β-diketones and β-ketonic

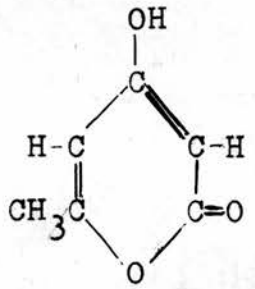
esters were prepared and their light absorption was compared with that of the enol acetate of γ-phenyl tetronic acid. From measurements of the light absorption properties of enol acetates (cf. A. E. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy in Organic Chemistry", Arnold, London, 1954, p.99) the effect of enol acetylation is to neutralise the bathochromic effect of the hydroxyl group, thus causing the compound to show only the absorption expected of a simple αβ-unsaturated ketone. E.g. R. S. Rasmussen, D. D. Tunicliff and R. R. Brattain (J.Am.Chem.Soc., 1949, 71, 1069) showed that the enol acetate of acetylacetone shows maxima at 2300A. (ε 43,000) and 3250A. (ε 60) as would be expected for an αβ-unsaturated ketone.

The enol acetate of dimedone in ethanol showed maxima at 2820A. ($\varepsilon_{max.}$ 3,600) and at 2340A. ($\varepsilon_{max.}$ 9,600). The latter can be compared with the absorption maximum of 3-methyl cyclohexenone at 2350A. (L. K. Evans and A. E. Gillam, J.Chem.Soc., 1941, 816). This hypsochromic displacement was parallelled by that shown in the case of the enol acetate of ethyl acetoacetate in ethanol. Here, no maximum was observed but only a general increase in intensity of absorption at shorter wavelengths. The comparison may be made with crotonic acid which has λ max 204 ($\varepsilon_{max.}$ 11,500) (K. W. Hausser, R. Kuhn, A. Smakula and M. Hoffer, Z.physikal.Chem., 1935, B29, 371)

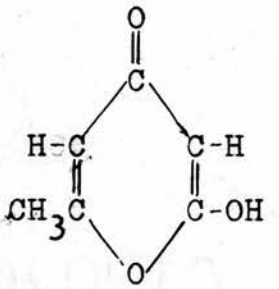
Such general absorption was also shown by the enol acetate of γ-phenyl tetronic acid in cyclohexane as would have been expected from the previous observations.

The compounds next chosen for study were 6-methyl pyronone, its methyl ether and its enol acetate. It was thought that these compounds might show some resemblance to the tetronic acids, but the light absorption properties are very different (v. Table I). The absorption maximum of 6-methyl pyronone in alkaline solution shows a slight hypsochromic displacement on ionisation in contrast to the large bathochromic displacement observed in the spectra of the tetronic acids when ionisation takes place.

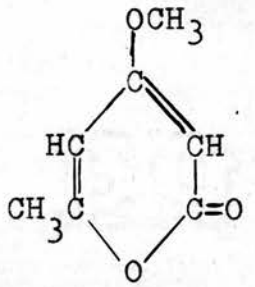
Table I.	λ	ε
6-Methyl pyronone in methanol	282	7,100
6-Methyl pyronone in water	281	7,900
	345	30
6-Methyl pyronone in NaOH solution	275	9,600
6-Methyl pyronone methyl ether in methanol	279	6,350
6-Methyl pyronone enol acetate in methanol	290	5,930



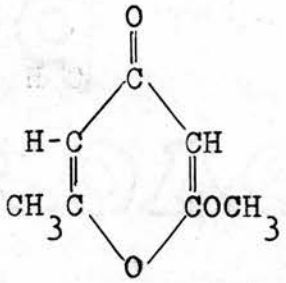
[Ia]



[Ib]



[IIa]



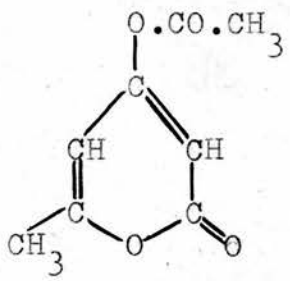
[IIb]

These figures are in agreement with those of J. A. Berson (J.Am.Chem.Soc.,1952,74,5772). The similarity of the spectrum of 6-methyl pyronone to that of the parent compound shows that the latter must exist in the enolic form as [Ia] or [Ib]; and the methyl ether (It has only proved possible to prepare one ether) must therefore be derived from an ∝-pyrone [IIa] (F. Sproxton, J.Chem, Soc.,1906,1189) or a γ-pyrone [IIb] (F. Arndt and B. Avan, Ber.,1951,84,343).

2:6-Dimethyl-γ-pyrone was prepared and showed a maximum at 2450A. ($\varepsilon_{max.}$ 16,100)in ethanol which bears no resemblance to the pyronone spectra. 5-Methyl-∝-pyrone in ethanol shows a maximum at 3000A. (ε 5,010) (R. C. Elderfield and J. Fried, J.Org.Chem,,1941,6,566)

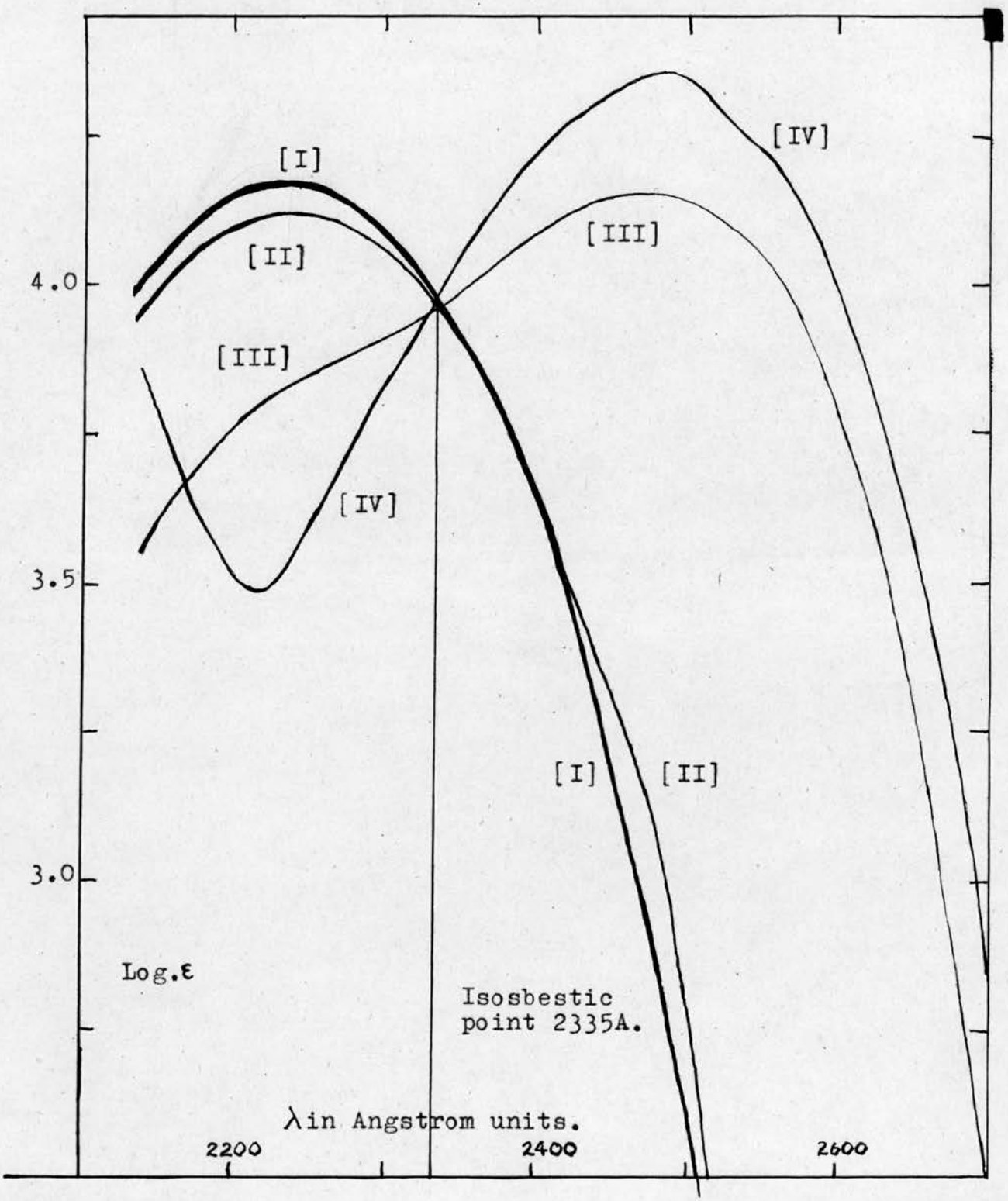
and in intensity this band is closer to the pyronone spectra but is displaced towards the red.

The enol acetate of 6-methyl pyronone has $\lambda_{max.}$ 2900Å. ($\varepsilon_{max.}$ 5,930) in methanolic or ethanolic solution, showing that if, as would be expected by anology with other compounds, enol acetylation here neutralises the effect of a hydroxyl group such an effect must be hypsochromic and not bathochromic. Such neutralisation brings us closer to the absorption of the α-pyrone type of compound strongly suggesting that the enol acetate is [III] derived from [Ia] rather than [Ib].



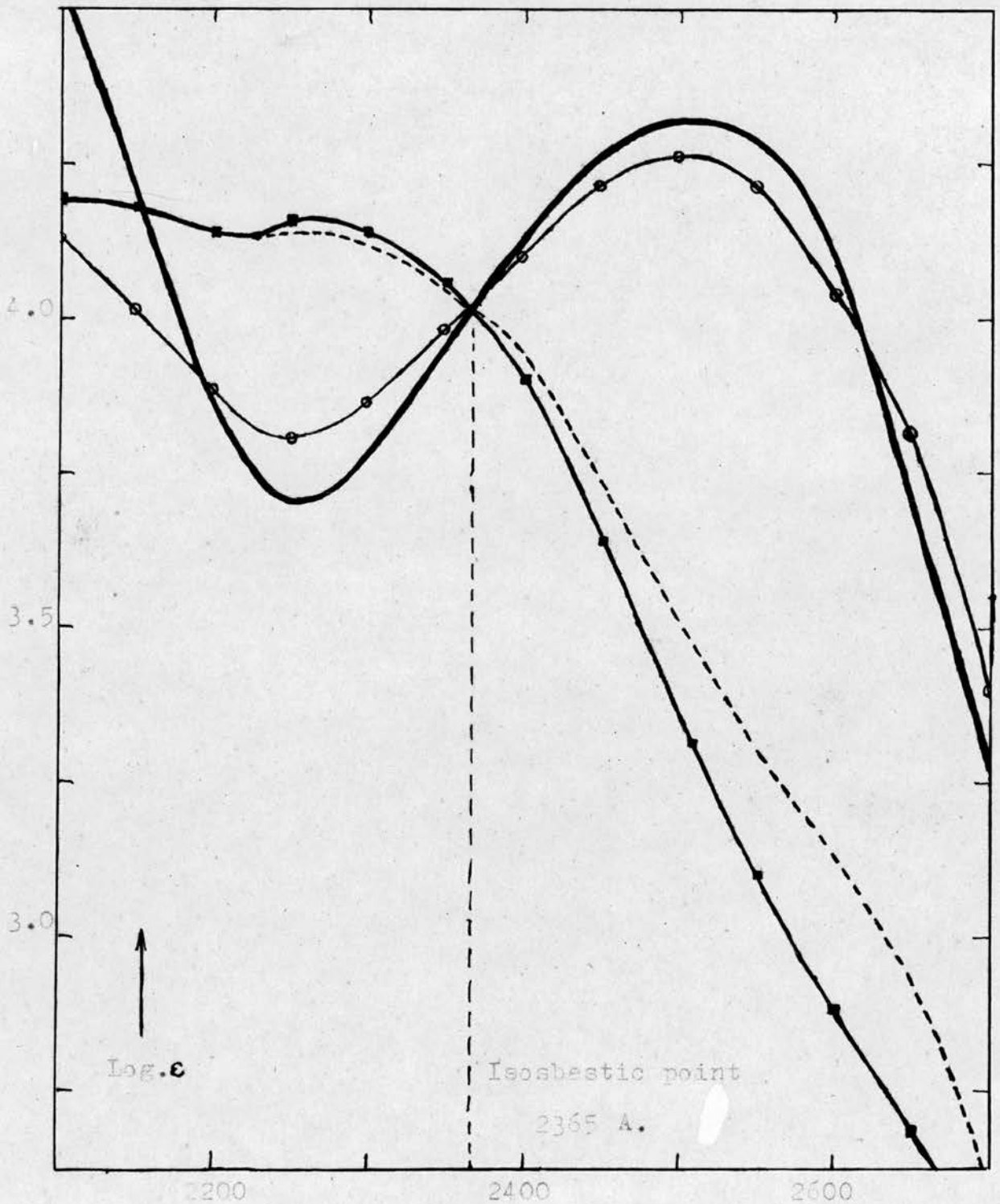
[III]

U. V. ABSORPTION SPECTRA

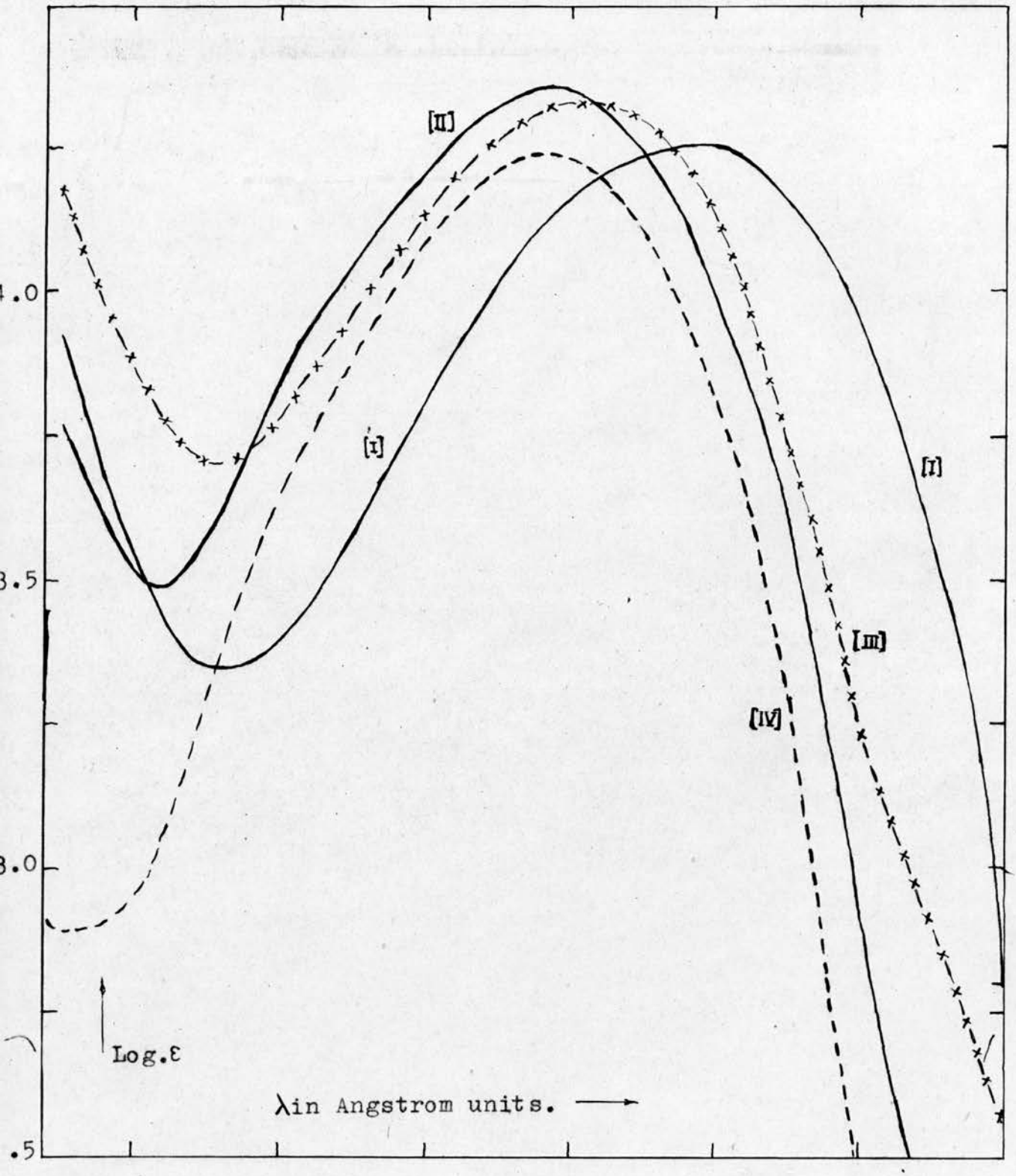


U.V. Absorption curve of tetronic acid in 80% aqueous ethanol at various pH values.

[I] pH 1.2 ; [II] pH 2.2 ; [III] pH 5.6 ; [IV] pH 13.5.



U.V. absorption spectrum of γ-phenyl tetronic acid in aqueous solution.

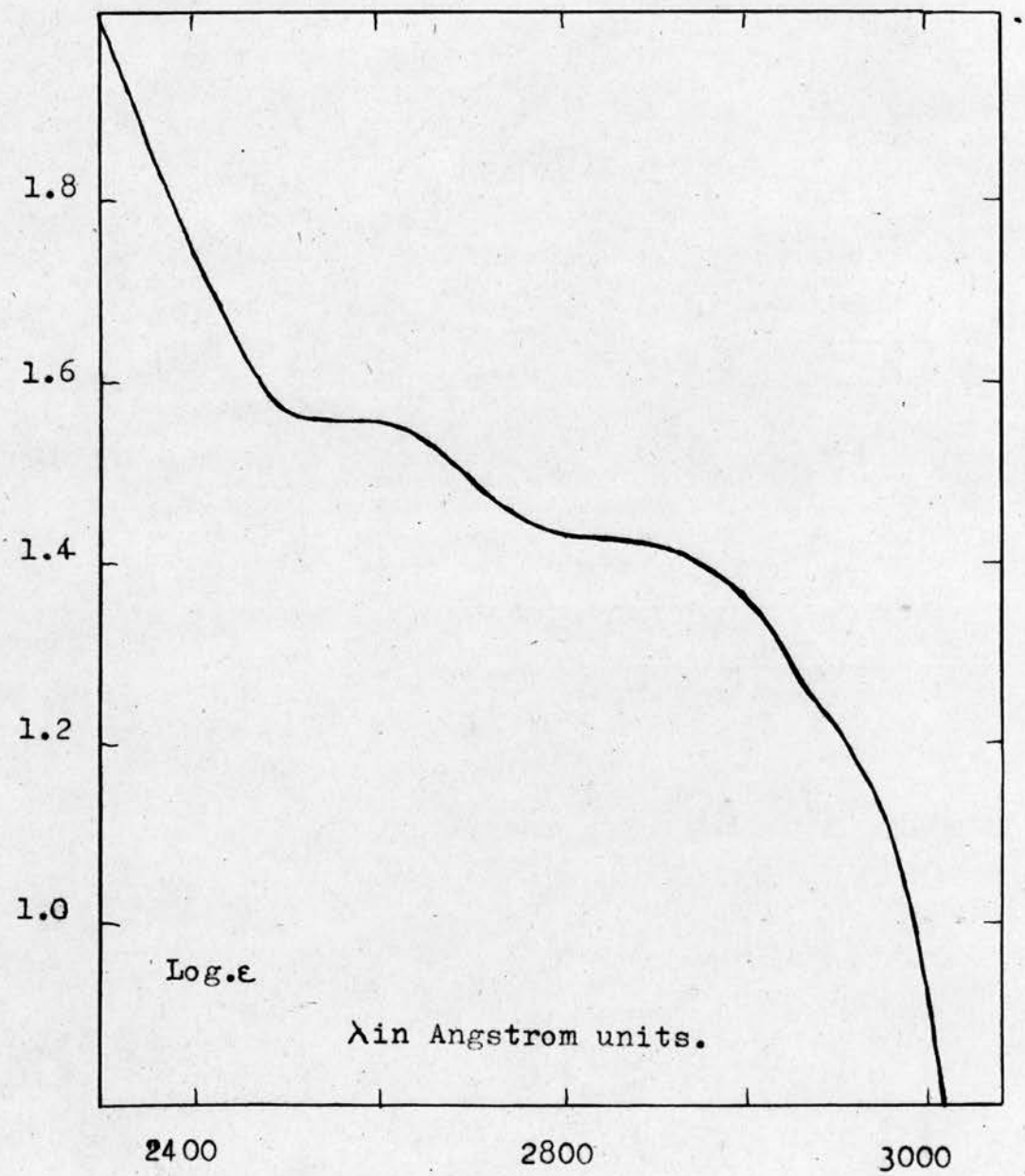


'etronic acid U.V. absorption curves showing effect of ∝ and γ
-ubstituents. [I] ∝-Ethyl tetronic acid in ethanol with NaOEt.

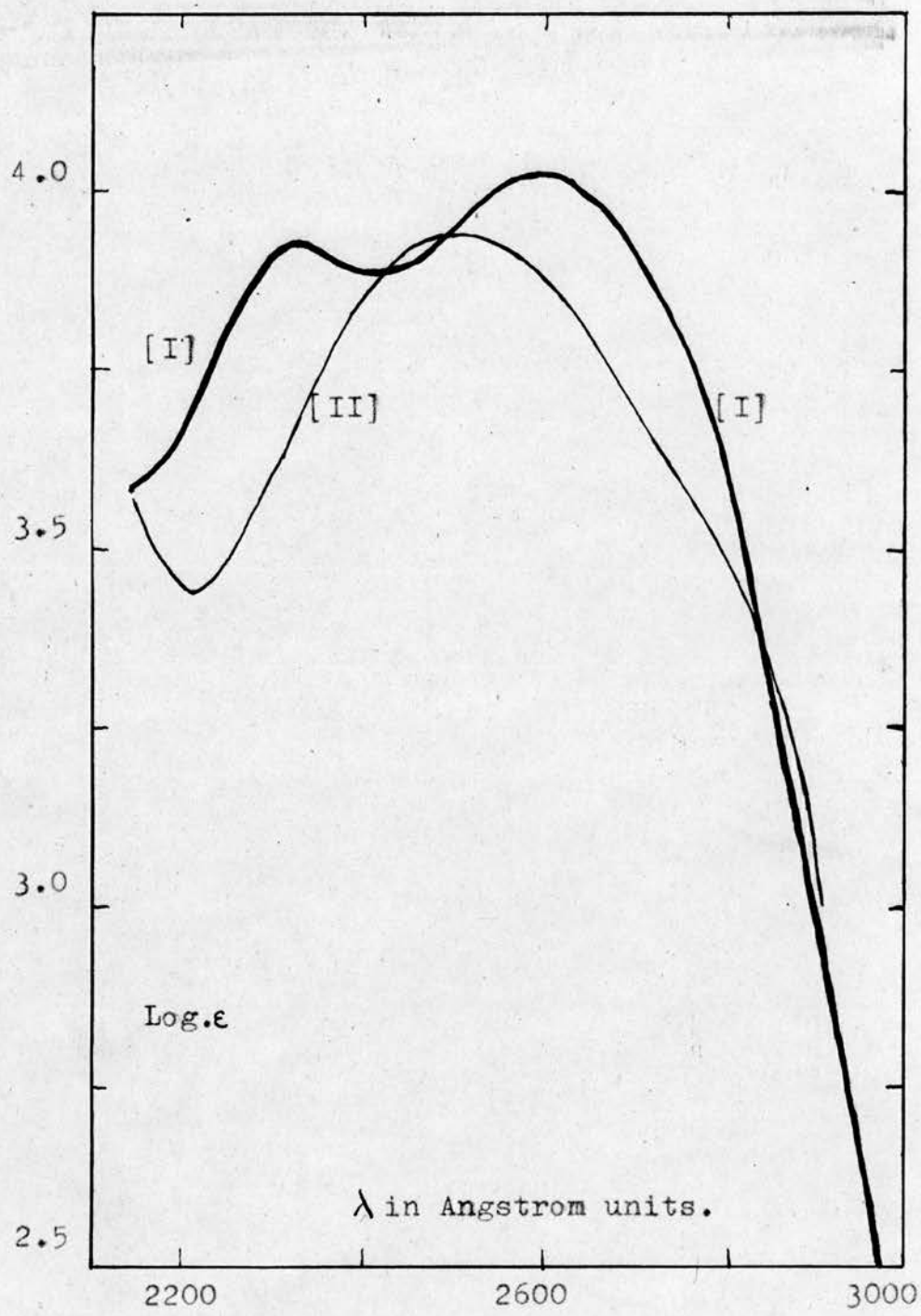
[II] Tetronic acid in 80% aqueous ethanol.

—x—x— [III] γ-Phenyl tetronic acid in aqueous NaOH solution.

— — — [IV] γ-Cyclohexyl tetronic acid in ethanol with NaOEt.



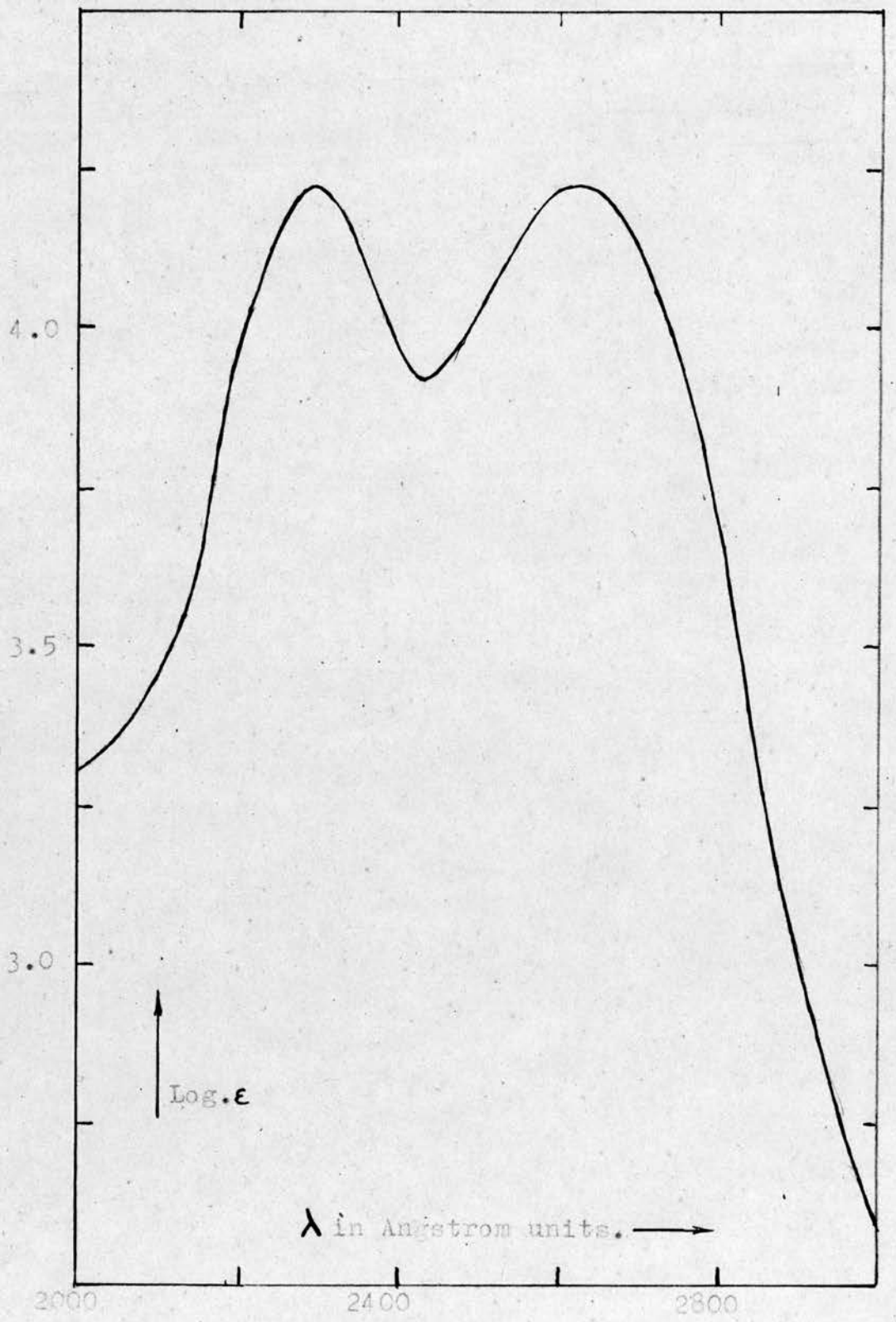
U.V. absorption of ∝∝-dimethyl-β-ketobutyrolactone in ethanolic solution. [11.39g./1.]



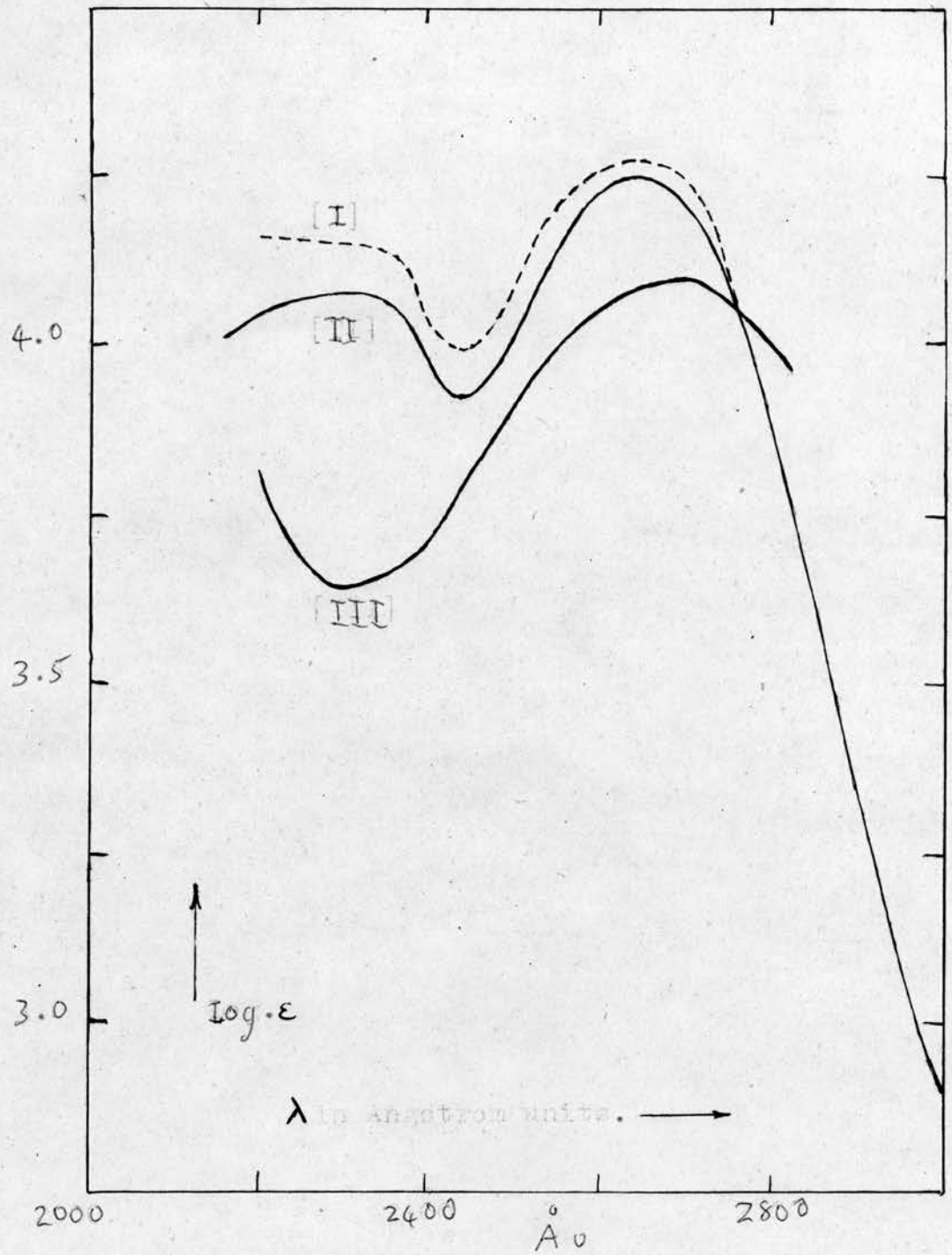
U.V. spectrum of synthetic carolinic acid.

[I] In ethanolic solution.

[II] In ethanolc solution containing hydrochloric acid.



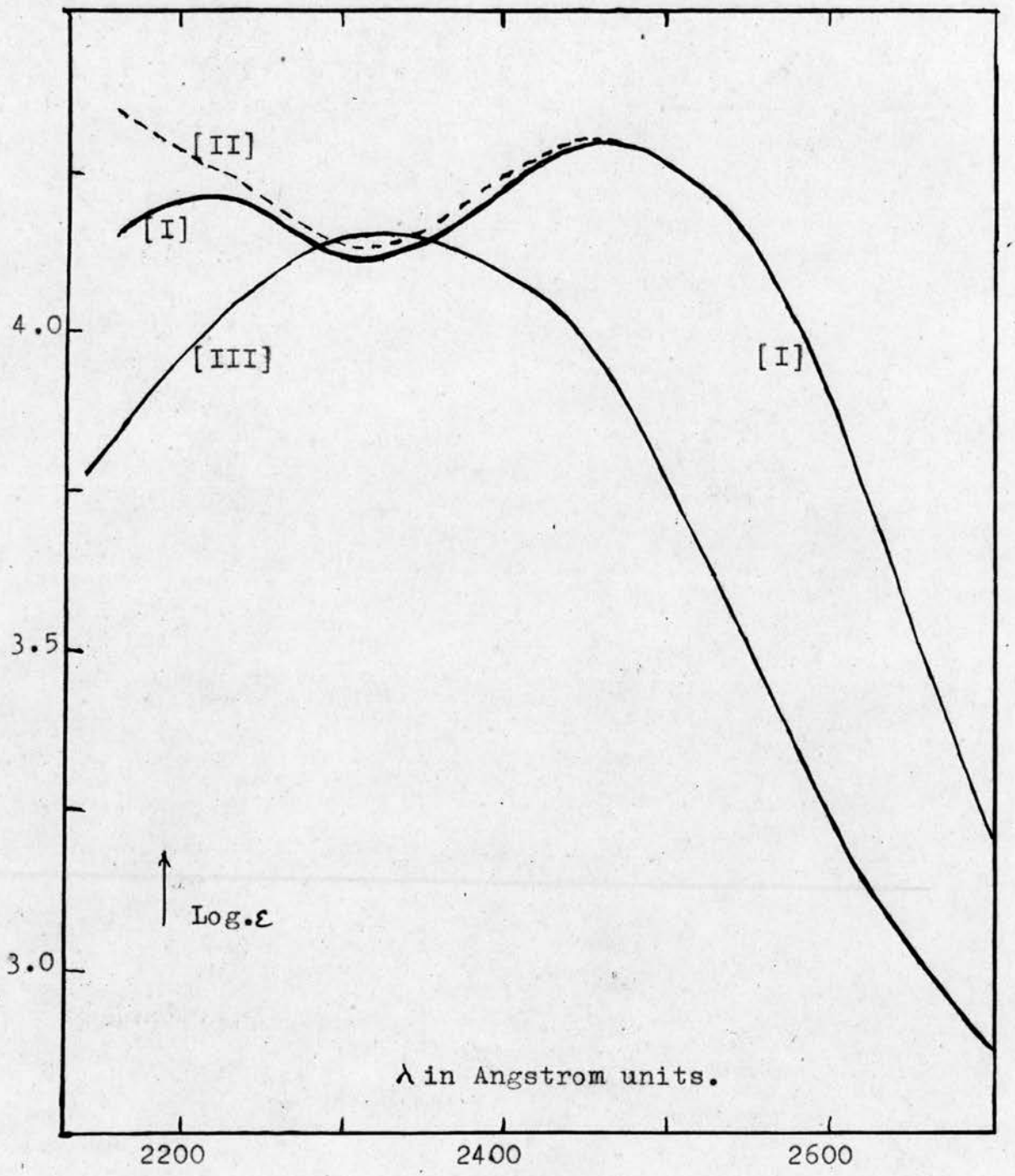
U.V. absorption spectrum of synthetic carolinic acid in aqueous solution.



U.V. absorption spectrum of ∝-acetyl-γ-phenyl tetronic acid in ethanolic solution.[II].

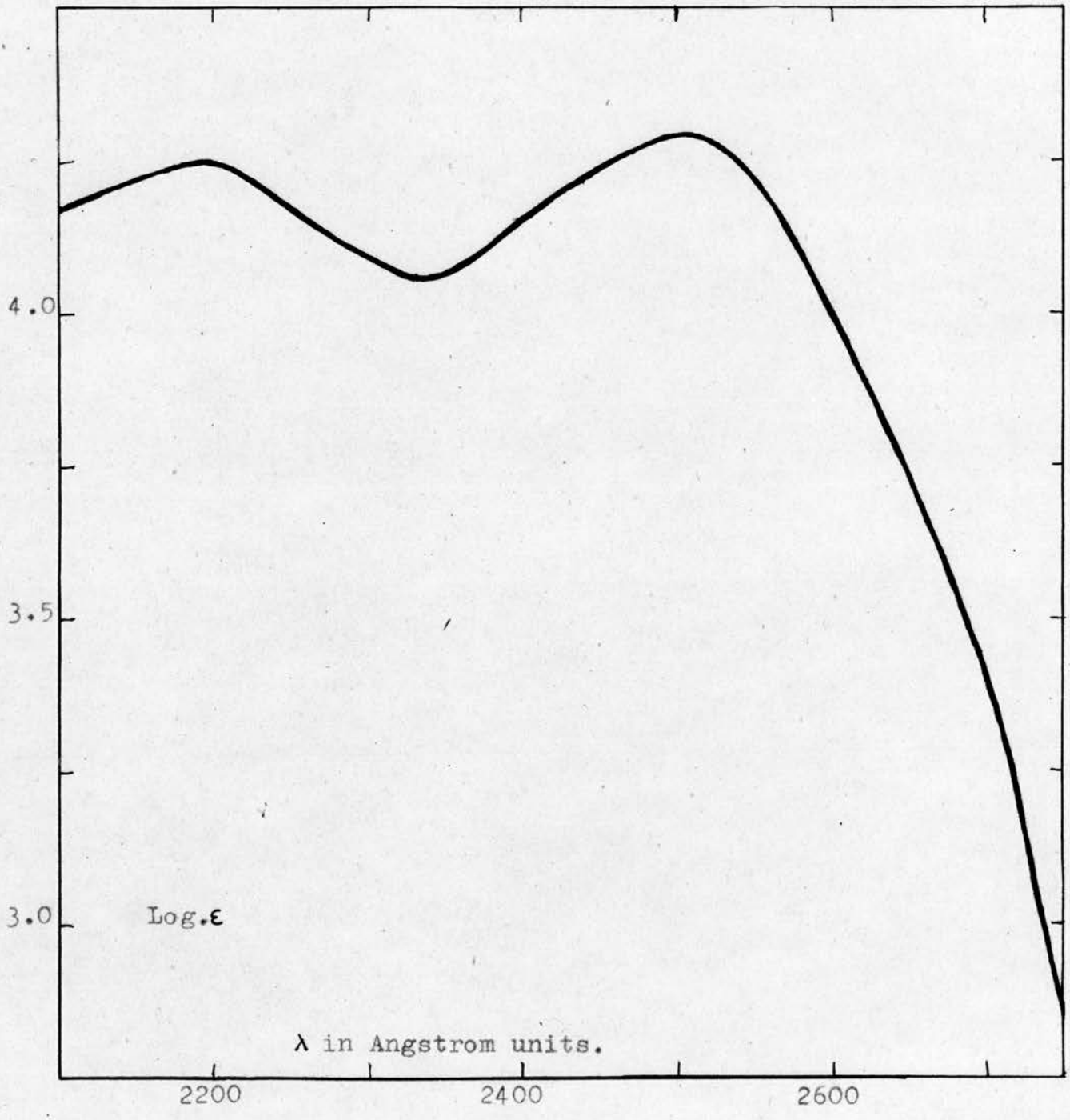
Curve [I] (dotted): sodium ethoxide added to solution.

Curve[III]: hydrochloric acid added to solution.

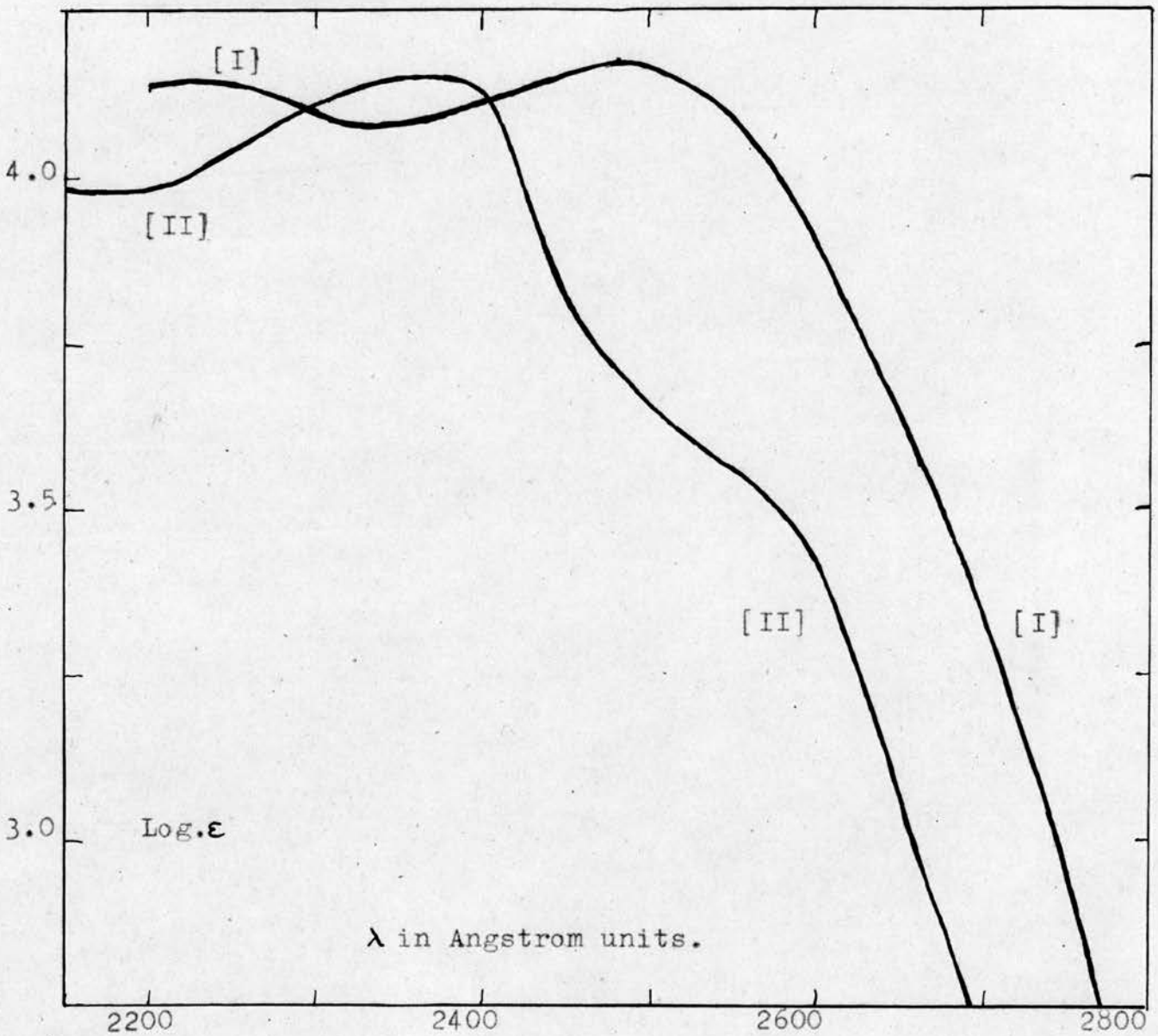


U.V. absorption spectrum of ∝-carbethoxy tetronic acid.

[I] In ethanolic solution.
[II] In ethanolic solution with sodium ethoxide.
[III] In ethanolic solution containing hydrochloric acid.



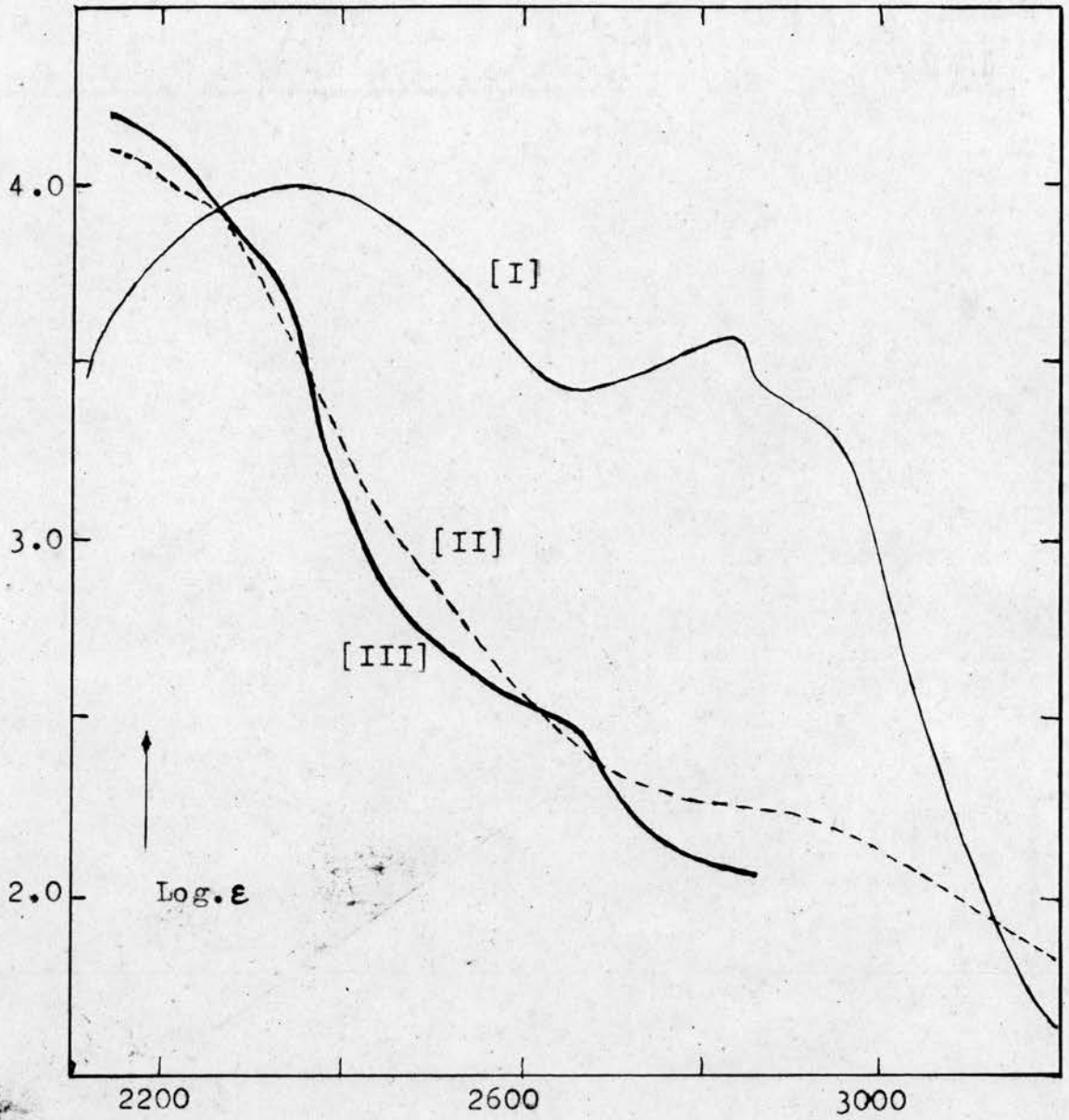
U.V. absorption spectrum of α-carbethoxy-γ-phenyl tetronic acid in aqueous solution . (Unchanged on addition of acid or alkali.)



U.V. absorption spectrum of α-carbethoxy-γ-phenyl tetronic acid.

[I] In ethanolic solution.

[II] In ethanolic solution containing hydrochloric acid.

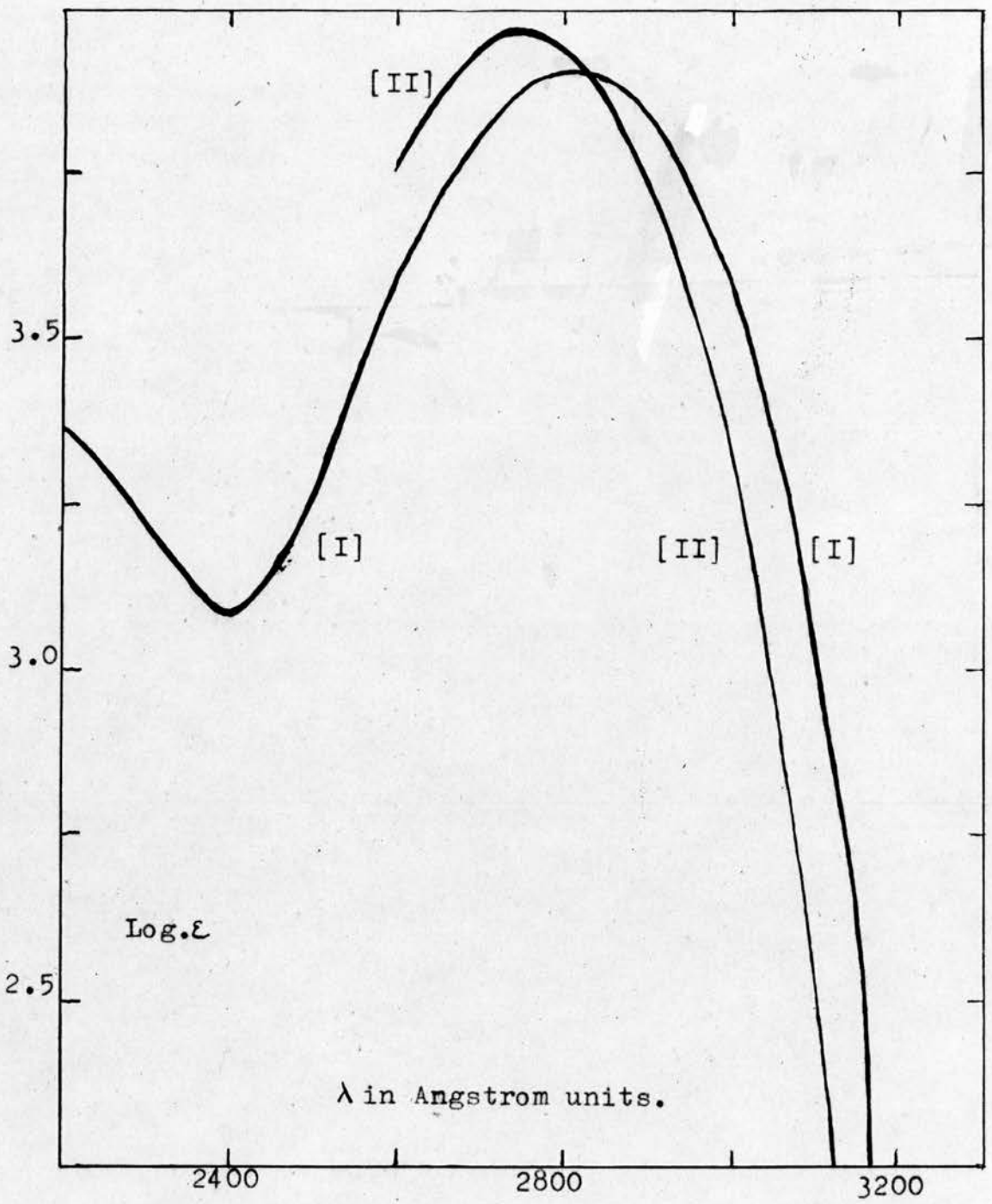


U.V. absorption spectrum of enol acetates:-

5:5-dimethylcyclohexane-1:3-dione enol acetate in ethanolic solution [I].

Ethyl β-acetoxycrotonate in ethanolic solution [II].

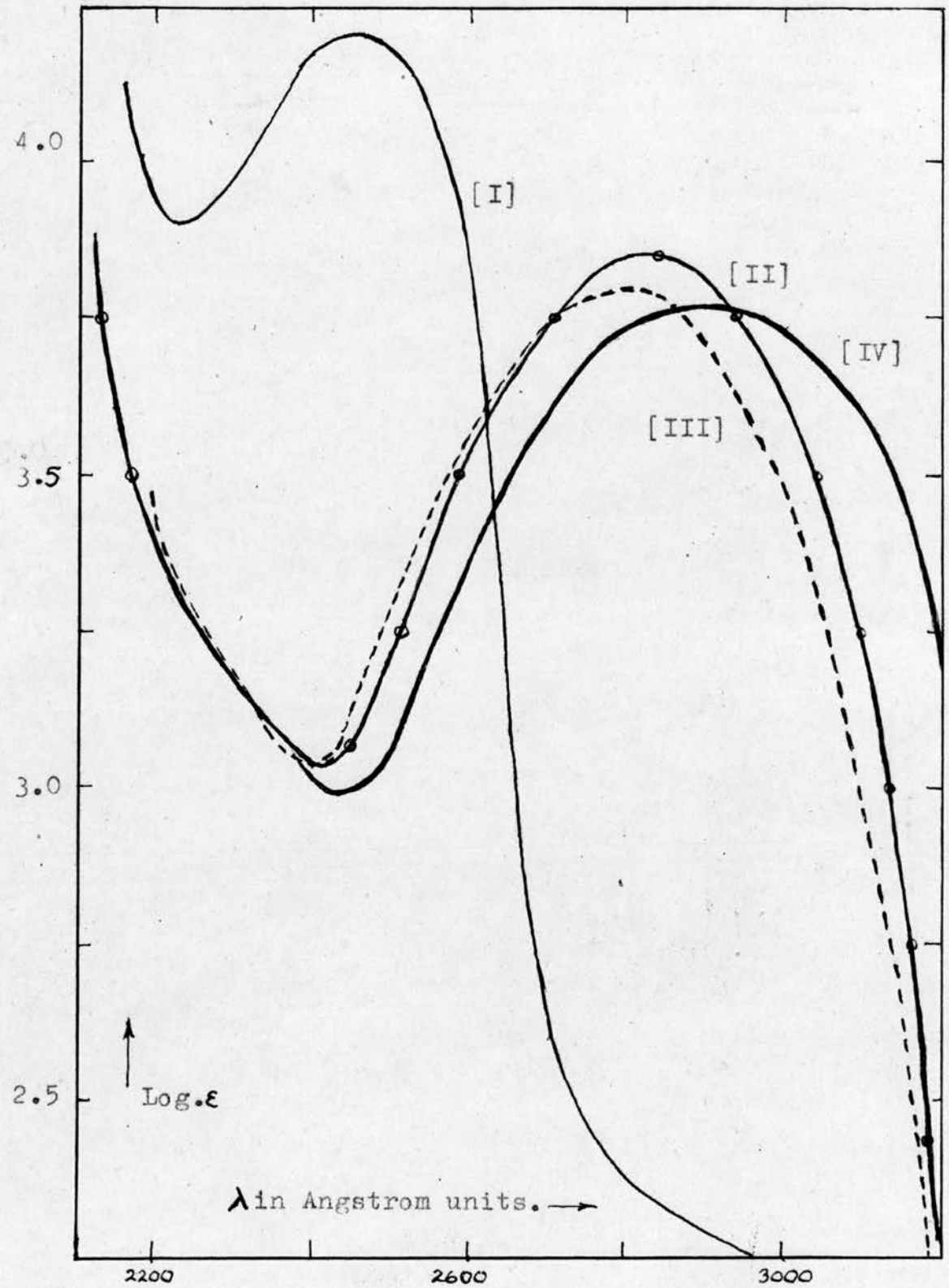
γ-Phenyl tetronic acid enol acetate in cyclohexane [III].



U.V. absorption spectrum of 6-methyl pyronone showing effect of ionisation.

[I] 6-Methyl pyronone in aqueous solution.

[II] 6-Methyl pyronone in N/25 NaOH solution.



Curve [I] —— 2:6-dimethyl-γ-pyrone in ethanolic solution.
Curve [II] —o— 6-methyl pyronone in ethanolic solution.
Curve [III] --- 6-methyl pyronone methyl ether in methanol
Curve [IV] —— 6-methyl pyronone enol acetate in ethanol.

U.V. absorption spectra of 6-methyl pyronone and some related compounds.

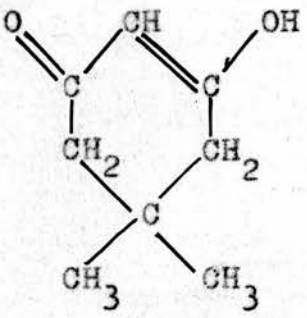
DISCUSSION

DISCUSSION

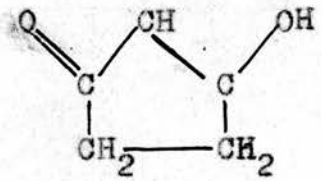
Tetronic acid possesses the structure I, tautomeric with II. Tetronic acids are strongly acidic and the acidity is due to the mesomeric system HO-C=C-C=O which is a vinylogue of the carboxyl group. The inclusion of the β-diketonic system in a ring appears to stabilise the enolic form in some cases (as in cyclohexane-1:3-diones) and tetronic acids appear to be enolic in polar solvents and to contain a considerable proportion of enolic form in non-polar solvents. This may not be so at very low orders of concentration in non-polar solvents, where inter-molecular interaction is negligible. The very low solubility in non-polar solvents of all the tetronic acids discussed in the experimental section of this thesis has been an obstacle to measurements over a range of concentrations. In order to surmount this difficulty, experiments are in hand for the synthesis of a tetronic acid possessing a large γ-alkyl group, which, it is hoped, will render the material more soluble in non-polar solvents in order to facilitate observations on the ultra-violet spectrum at accurately messured concentrations.

The strong acidity of tetronic acid must arise from several factors: (i) A greater number of resonance structures can contribute to the energy of the anion than in the case of the undissociated acid, therefore the former will be

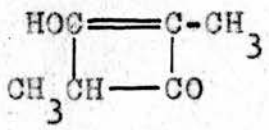
stabilised relative to the latter, (ii) Impossibility of internal hydrogen bonding. In compounds such as ethyl acetoacetate and acetylacetone the inclusion of the enolic hydrogen atom in a six membered chelate ring reduces the acid strength but in tetronic acids steric requirements make such internal hydrogen bonding impossible; (iii) The size of the ring. Ring size seems to have an important bearing on the acidic strength of a β-diketonic system fused in that ring. For analogues of tetronic acid no figures are available but a clear view of this tendency is given by the following carbocyclic compounds:



pK_a 5.25 (G. Schwarzenbach and E. Felder, Helv.Chim.Acta,1944,27,1701)



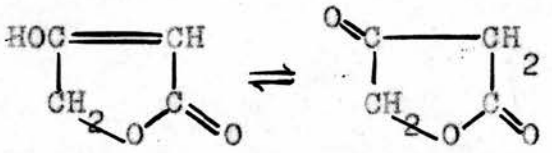
pK_a 4.5 (J. N. Boothe, M. G. Wilkinson, S. Kushner and J. H. Williams, J.Am.Chem.Soc.,1953,75,1732)



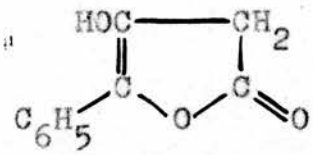
pK_a 2.8 (R. B. Woodward and G. Small, J.Am.Chem.Soc.,1950,72,1301)

Although tetronic acids possess the enolic form it is not possible to correlate the proportion of the enolic form

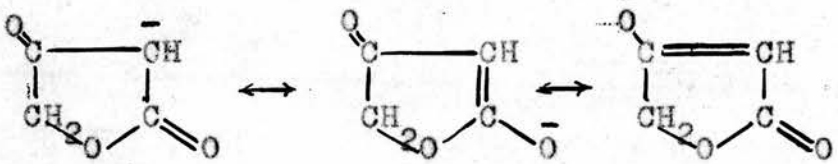
present with the acidity of a compound, as Claisen's rule that there is a proportionality between enol content and acidity of a keto-enol system has been disproved by G. Schwarzenbach and E. Felder (loc.cit.). In the ion a form such as III can make an important contribution to the resonance. Structures of this type with charge on the α-carbon atom have been neglected by W. D. Kumler in his discussion of resonance forms (J.Am.Chem.Soc.,1940,62,3292), but must possess some importance as this position is readily attacked by electrophilic reagents.



[I] [II]

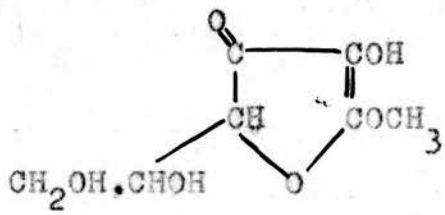


[VII]



[III] [IV] [V]

[VI]



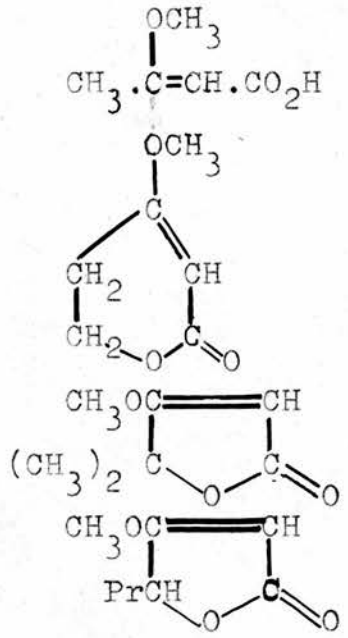
[VIII]

The double bond in the tetronic acids appears always to be conjugated with the carbonyl group of the lactone system and attempts to obtain evidence of conjugation with a group in the γ-position, even such a powerfully conjugating group as phenyl, to give a βγ-unsaturated lactone [VII] have been unsuceessful. In this, these compounds differ from the simple crotonolactones, where the change from γ-phenyl-αβ-crotonolactone to γ-phenyl-βγ-crotonolactone readily takes place and the latter is the more stable form.

No evidence of a 1:3-dihydroxy-furan type of structure [VI] has been obtained. This type of structure might have been postulated to explain some of the properties of tetronic acids such as their stability to alkali and the ready electrophilic attack at the α position to give a substitution product. The only example of a tetronic acid derivative in which this type of enolisation tends to occur is a compound formulated as [VIII], an ascorbic acid derivative (W. N. Haworth, E. L. Hirst, F. Smith and W. J. Wilson, J.Chem.Soc.,193 ,829). Moreover, tetronic acids which have two alkyl groups in the γ-position behave as normal tetronic acids demonstrating that any electronic effects transmitted through the γ-position must be purely of the inductive type.

The main features of the ultra-violet absorption spectra of the tetronic acids have been summarised and

comparison with the corresponding acyclic systems and also with δ-lactones shows the points of difference (Methyl ethers are used for comparison in order that hydrogen bonding effects are absent).



	$\lambda_{max.}$	ε	
$CH_3.C(OCH_3)=CH.CO_2H$	2340	13,500	(L. N. Owen, J.Chem, Soc.,1945,385)
	2330	13,500	(E. R. H. Jones and M. C. Whiting, J. Chem.Soc.,1949,1423)
$CH_3OC=CH$ $(CH_3)_2C$ $CH_3OC=CH$	2180	17,000	do.
PrCH	2210	13,500	do.

The suggestion of E. R. H. Jones (loc.cit.), that an alternative inductive path through the γ-carbon atom reinforces the normal electron drift away from the β-carbon atom through the tautomeric path, appears to explain the facts. The effect would be rapidly damped out in a six membered ring and would account for the difference in spectra. Unfortunately no figures are available for the acidic dissociation constants of such compounds so that the effect here cannot be compared, in order to ascertain whether the dissociation constant of the δ-lactone is approximately the

same as that of cyclohexane-1:3-dione. This might be expected if the factor responsible for the increase in pKa value on passing from cyclopentane-1:3-dione to tetronic acid is purely the inductive effect of the oxygen atom.

The general increase in electron availability within the ring system must account for the resistance of tetronic acids to alkaline hydrolysis (see experimental section).

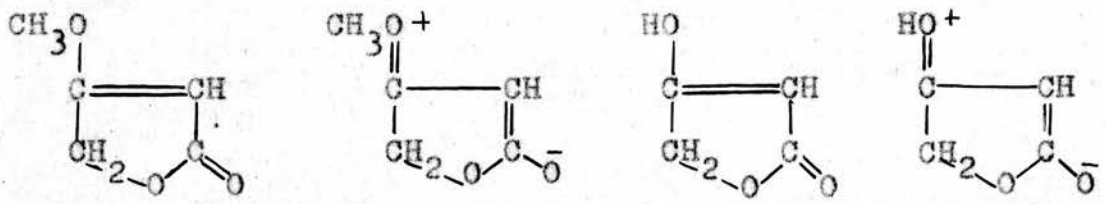
The shift of the absorption band of tetronic acid to longer wavelengths on ionisation is due to the negative charge on the enolic oxygen atom which enables its 'lone pair' of electrons to associate with the other π electrons of the HO-C=C-C=O system. This may also be described as resonance between structures III, IV and V.

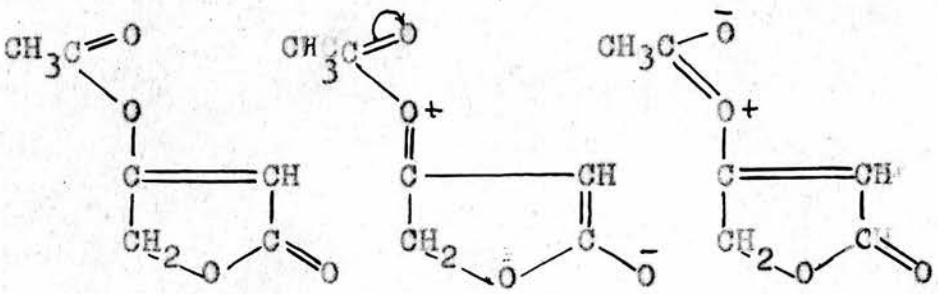
That methylation is accompanied by little change in ultra-violet absorption compared with acetoacetic ester is in accordance with absence of hydrogen bonding in the molecule. In acetoacetic ester a shift of 90A. towards the violet on methylation is associated with prevention of hydrogen bonding.

The analogy between the undissociated enol and the methyl ether is clear when the structures [IX]-[XI] and [I] which can participate in resonance are written. The effect of H and CH_3 on the 'lone pair' of oxygen electrons will not be very different. In the same manner the neutralisation of the chromophoric effect of the oxygen attached to -C=C-CO-, by an acetyl group is explicable, in that a structure such as [XIII] is very umlikely as

the carbon atom of the acetyl >CO group will tend to possess some positive charge and structures with like charge at both ends of a linkage would be of such high energy as to have little part in resonance. In [XIV] the 'enol' oxygen is positively charged and such a structure will completely prevent the 'lone pair' of electrons of the oxygen atom from interacting with the C=C-CO system as they are involved in the double bond between the oxygen atom and the carbon atom of the acetyl >CO group.

[IX] [X] [I] [XI]





[XII] [XIII] [XIV]

The spectra of α-acetyl and α-carbethoxy substituted tetronic acids is quite characteristic and shows a doubly banded spectrum typical of an enolised β-triketone. This system must be hydrogen bonded (indeed this effect has been shown by infra-red absorption spectrum measurements L. A. Duncanson, [J.Chem.Soc.,1953,1207]) and although the tendency of hydrogen bonding is to diminish the acidity of enolic systems, these compounds are more strongly acidic than the unsubstituted tetronic acids (e.g. α-carbethoxy- γ-phenyl tetronic acid has pK_a 3.35).

Ionisation has very little effect on the spectra of these compounds which remain fundamentally the same in acidic and alkaline media, with some increase of extinction coefficient in the latter. Acetoacetic ester which contains a chelate ring does show increase in wave length of absorption at higher pH values as, on account of its weak acidity, a higher pH is required to convert it to the ionic form. However, at pH values at which the compounds must be completely ionic the acetyl tetronic acids possess substantially the same absorption spectrum as the unionised form with a slightly greater intensity. It is difficult to postulate a reason for this, we might infer that the oxygen atom involved in the ionisation plays no part in the chelate ring system which must be responsible for the characteristic spectrum of the compound (a change from a chelate to a non-chelated system

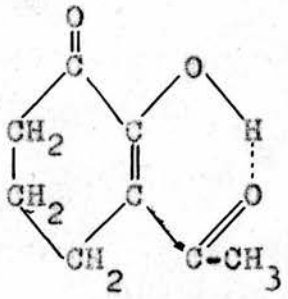
involves a change in the absorption maximum of a compound as already noted for the methylation of ethyl acetoacetate which produces a shift of 90A. towards the violet, cf. the displacement on ionisation of ethyl acetoacetate which is from 2450A. to 2770A. = 320A. [P. Grossmann, Z.physikal. Chem.,1924,109,305]).

H. Smith (J.Chem.Soc.,1953,803) has determined the ultra-violet absorption spectrum of 2-acetylcyclohexane-1:3-dione in ethanolic solution and has suggested that with an acidic compound of this type, which would be expected to show concentration dependent absorption, mineral acid should be added to the solvent to prevent dissociation and to show the true absorption of the undissociated compound. However, it was found that the absorption spectra of acetyl tetronic acids show almost the same maxima in alcoholic as in aqueous solution, but in the latter the addition of acid or alkali does not substantially affect the position or intensity of the absorption bands, whereas a profound effect was observed in ethanol containing a little concentrated hydrochloric acid (solution was ca. N/10), with all the compounds investigated (α-Acetyl-γ-phenyl tetronic acid, α-carbethoxy-γ-phenyl tetronic acid, α-carbethoxy tetronic acid and synthetic carolinic acid). In place of the usual doubly banded spectrum was observed only a singly banded spectrum with maxima at wavelengths: 2340A. (α-carbethoxy

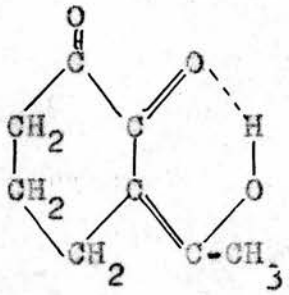
tetronic acid) 2370A. (∝-carbethoxy-γ-phenyl tetronic acid) 2500A. (carolinic acid) and 2700A. (∝-acetyl-γ-phenyl tetronic acid).

It is obvious that care is required in measuring the spectra of such compounds under conditions when it might be presumed that the sole effect of addition of acid would be to decrease ionisation, for clearly some more fundamental effect is indicated.

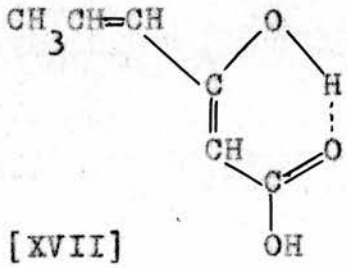
H. Smith (loc.cit.) has suggested that the enolised β-triketonic system owes its two absorption bands at 2350A. and 2750A. to the absorption of an ∝β-unsaturated ketonic system [XV] and to that of a butadienoid type [XVI] respectively.



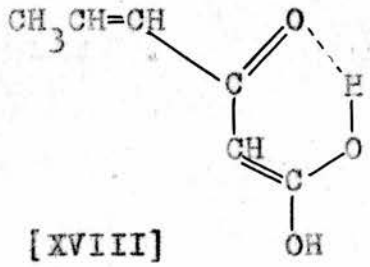
[XV]



[XVI]



[XVII]



[XVIII]

This type of argument might be extended to tetronic acids where analogous structures can be written and thus held to account for the two absorption bands but to allot absorption bands to structures which participate in resonance on the basis of purely empirical reasoning may be a misleading procedure e.g. in β-hydroxysorbic acid which has a singly banded spectrum $\lambda_{max.}$ 2,800 ($\varepsilon_{max.}$ 6,500) but two analogous structures can be written as [XVII] and [XVIII] where cross-conjugation of a C-C double-bond with a 6-membered chelate ring occurs.

The reactions of the tetronic acids agree only qualitatively with the electron displacements suggested by E. R. H. Jones and M. C. Whiting (J.Chem.Soc.,1949, 1423) but a comparison with γ-ethoxyacetoacetic ester, where the same effects, inductive and mesomeric, are operative and where the only fundamental difference is the incorporation of the keto-enol system in this compound in a chelate ring, shows that the five membered ring lactone must be fundamentally different from a straight chain compound when the lactone incorporates a conjugated enolic system, as exemplified in the resistance of the tetronic acids to hydrolysis, in their high acidity and in their reactions with electrophilic reagents which are almost analogous to those of a phenol.

SUMMARY.

1) The chemistry, constitution and properties of the tetronic acids and their naturally occurring derivatives have been reviewed. The question of keto-enol equilibrium was discussed but it was concluded that this cannot be finally decided until more accurate observations are made such as thoseon the absorption spectra of the compounds in non-polar solvents.

2) Previous methods of synthesis of the tetronic acids have been repeated and new methods have been devised, of which the most successful generally applicable method was found to be the condensation of a substituted acid chloride with an organometallic compound formed by reaction of magnesium ethoxide with diethyl malonate or a β-keto ester. In this manner tetronic acid and γ-phenyl tetronic acid were prepared and the mould metabolic product, DL-carolinic acid, was synthesised. The structure of DL-carolinic acid was thus established as α-(β-carboxy-propionyl)-γ-methyl tetronic acid.

3) The ultra-violet absorption spectra of some tetronic acids, their derivatives and several related compounds have been studied. The light absorption of the tetronic acids showed concentration dependence ascribed to

ionisation and from the absorption curves, values of the dissociation constant were derived. Tetronic acids bearing an α-carbonyl substituent showed characteristic doubly banded spectra in aqueous or ethanolic solution but addition of mineral acid to the latter caused appreciable modification, only a single band being then observed.

4) The results obtained have been discussed and analogies drawn with other β-ketonic compounds which, however, do not possess the same remarkable stability. In their reactions the tetronic acids were considered to be in many ways analogous to phenolic compounds.

ACKNOWLEDGEMENTS.

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