TETRONIC ACIDS

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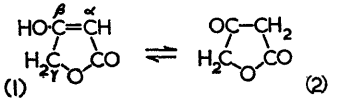
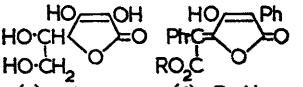
TETRONIC ACIDS are α- or γ-substituted derivatives of the parent acid (1). This form normally predominates in the tautomeric system (1) ⇌ (2): non-enolisable forms, *i.e.*, those disubstituted in the α-position, are not regarded as tetronic acids and possess very different properties; they are commonly liquids, have no acidic properties, and the lactone ring is easily opened by hydrolysis.[1] In general, the group is characterised



(1) (2)

by the stability of the nucleus, the strongly acidic nature of its members, and the susceptibility of the nucleus to electrophilic substitution in the α-position (if unsubstituted). In this respect it shows some resemblances in behaviour to that of the phenols.[2] The group also shows many similarities to the cyclic 1,3-diketones and is much more stable to alkaline reagents than would be expected of a simple lactone or derivative of acetoacetic ester, of which it may be regarded as the cyclic analogue. Tetronic acid and its simple alkyl derivatives are polar substances of high melting point.

The tetronic acid nucleus occurs in a number of natural products. The most important of these is vitamin C (3) which is a γ-substituted α-hydroxytetronic acid.[3] A group of complex tetronic acid derivatives is found in the lichens as colouring matters. The most important of these are pulvinic (4) and vulpinic acids (5). Other members of this group are pinastrinic acid, calycin, epanorin, stictaurin, and coniocylic acid.[4]

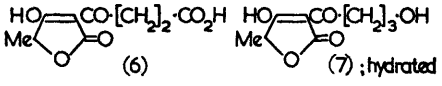


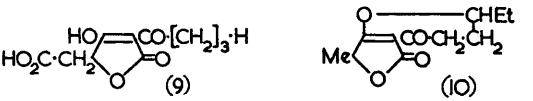
(3) (4); R=H (5); R=Me

Tetronic acid derivatives are also found as mould metabolic products. Raistrick and his co-workers[5] have isolated a series of related tetronic acids—carolinic (6), carolic (7), carlic (8), and carlosic (9) acids and also γ-methyltetronic acid from *Penicillium Charlesii* G. Smith, a mould

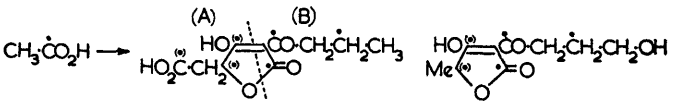
[1] Conrad and Gast, *Ber.*, 1898, **31**, 2726.
[2] Baker, Grice, and Jansen, *J.*, 1943, 241.
[3] Hirst, *Fortschr. Chem. org. Naturstoffe*, 1939, p. 132.
[4] For review, see Meyer and Cook, "The Chemistry of Natural Colouring Matters," Reinhold, N.Y., 1943, p. 156.
[5] Clutterbuck, Haworth, Raistrick, Smith, and Stacey, *Biochem. J.*, 1934, **28**, 94.

obtained from spoiled Italian maize. Birkinshaw and Raistrick[6] have also obtained terrestric acid (ethylcarolic acid) (10) from *P. terrestre* Jensen.



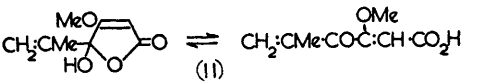


Studies on the biogenesis of carlosic and carolic acids from acetate have been made by Ehrensvärd, Lybing, and Reio[7] who have shown that the use of carboxyl-labelled acetate leads to the following labelling pattern:

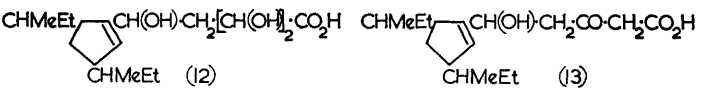


which strongly indicates that part of the molecule (B) is derived from three acetate residues whilst the part (A) is probably derived from another source related to the biosynthesis of carbohydrates. In this context it may be noted that zymonic acid, γ-carboxy-α-methyltetronic acid, is a metabolic product of glucose (see under).

Penicillic acid (11) was first isolated from culture filtrates of *P. puberulum*[8] and has since been found as a metabolic product of many other *Penicillium* species.



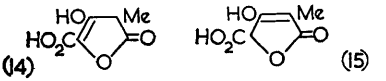
Kögl *et al.*,[9] in their work on plant-growth factors, isolated the materials auxin-a and auxin-b which they claimed were important as plant-growth hormones and to which they assigned the structures (12) and (13) respectively.



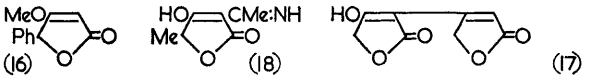
It appears that no other group of workers has been successful in obtaining these compounds. Jones and his co-workers[10] have synthesised some model compounds with structures related to those proposed by Kögl but these synthetic compounds showed no plant-hormone activity.

[6] Birkinshaw and Raistrick, *Biochem. J.*, 1936, **30**, 2194.
[7] Ehrensvärd, Lybing, and Reio, Chem. Soc. Symposium, Bristol, 1958, Chem. Soc., London, Special Pub. No. 12, p. 14.
[8] Alsberg and Black, *U.S. Dept. Agric. Bur. Plant Ind. Bull.*, 1913, No. 270.
[9] Kögl, Haagen-Smit, and Erxleben, *Z. physiol. Chem.*, 1934, **225**, 215.
[10] Henbest and Jones, *J.*, 1950, 3628; Brown, Henbest, and Jones, *J.*, 1950, 3634.

Zymonic acid, a metabolic product of the yeasts, *Trichosporon capitatum*, *Hansenula subpelliculosa*, and *Kloeckera brevis*, first isolated by Stodola and his co-workers,[11] was given the structure (14) but recent work has shown that it is the tetronic acid derivative (15).[12] The evidence leading to this re-formulation is discussed later (p. 309).



Apart from vitamin C and possibly the auxins, no tetronic acid derivatives appear to show any major physiological activity. However, several different types of activity have been recorded for tetronic acid derivatives: penicillic acid (11) is much more active against Gram-negative bacteria than penicillin, whilst the methyl ether of γ-phenyltetronic acid (16) is thirty times as active as penicillic acid;[13] vulpinic acid (5) possesses insecticidal properties;[14] anhydrotetronic acid (17)[15] has been shown to be active in stimulating the hatching of cysts of the potato eelworm (*Heterodora rostochiensis* Wollenberger); substituted tetronic acids have been



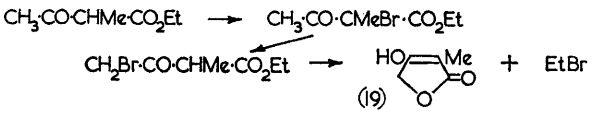
investigated with a view to enhancing their weak analgesic effect;[16] α-acetamido-γ-methyltetronic acid (18) is reported as having herbicidal action[17] and also as inhibiting chlorophyll production in several plants;[18] γγ-disubstituted derivatives were examined for narcotic activity but were found to be inactive;[19] γγ-disubstituted tetronic acids have been tested for hypnotic and anti-convulsant activities but activity was shown only at high doses.[20]

Methods of preparation

(1) *Cyclisation of γ-halogeno- and γ-acetoxy-acetoacetic ester derivatives.* The first preparation of a tetronic acid was by Demarçay,[21] who prepared α-methyltetronic acid (19) by heating the bromination (1 mol.) product of

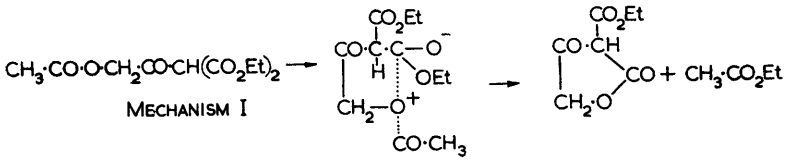
[11] Stodola, Shotwell, and Lockwood, *J. Amer. Chem. Soc.*, 1952, **74**, 5415.
[12] Haynes and Stanners, unpublished (see Stanners, Ph.D. Thesis, Edinburgh, 1956).
[13] Nineham and Raphael, *J.*, 1949, 118.
[14] Läuger, Martin, and Muller, *Helv. Chim. Acta*, 1944, **45**, 520.
[15] Calam, Todd, and Waring, *Biochem. J.*, 1949, **45**, 520.
[16] Reichert and Schäfer, *Arch. Pharm.*, 1958, **291**, 100.
[17] Rebstock and Sell, *J. Amer. Chem. Soc.*, 1952, **74**, 274.
[18] Hamner and Tukey, *Bot. Gaz.*, 1951, **112**, 525; Alamercy, Hamner, and Tukey, *Nature*, 1951, **168**, 85.
[19] Lecocq, *Compt. rend.*, 1946, **222**, 299.
[20] Cannon and Jones, *J. Org. Chem.*, 1958, **23**, 126.
[21] Demarçay, *Compt. rend.*, 1879, **88**, 126; *Ann. Chim. Phys.*, 1880, **20**, 433; Wedel, *Annalen*, 1883, **219**, 71.

α-methylacetoacetic ester:

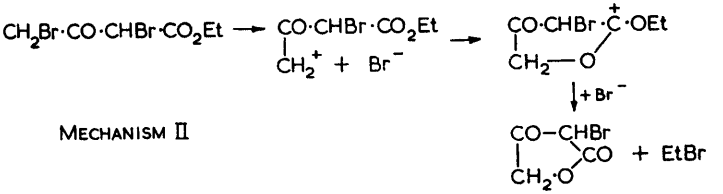


Later work has established that the reaction sequence is that shown, the initially formed α-bromo-compound rearranging to a γ-bromo-compound, which then cyclises by loss of ethyl bromide.[22]

Henecka[23] has suggested mechanisms I and II for the cyclisation of γ-acetoxy- and γ-bromo-compounds respectively:



MECHANISM I



MECHANISM II

However, it would be easy to write alternative mechanisms at least as plausible as those advanced by Henecka—for example, the formation of a tetronic acid from a γ-bromoacetoacetic ester could take place through an S_N2 mechanism—and it seems unprofitable to do so in the absence of kinetic data.

Tetronic acid itself cannot be prepared by this route, for ethyl γ-bromoacetoacetate does not cyclise on heating and it appears that an α-substituent is necessary for the reaction to proceed. No work has been done to establish why this is so but it is possible that the ease of cyclisation may depend on the enol form of the γ-bromo-β-keto-ester having both the ethoxycarbonyl and the bromomethyl groups in a *cis*-position and that in ethyl γ-bromoacetoacetate they are *trans*. This would be in accord with observations by other workers[24] on the difficulty of forming αβ-unsaturated lactones from *trans*-αβ-unsaturated hydroxy-acids. It should, however, be noted that claims have been made that benzyl γ-bromoacetoacetate can be cyclised with elimination of benzyl bromide to give tetronic acid, albeit in poor yield.[25] That the cyclisation need not proceed through the enol

[22] Hantzsch, *Ber.*, 1894, **27**, 255, 3168; Kharasch, Sternfeld, and Mayo, *J. Amer. Chem. Soc.*, 1937, **59**, 1655.

[23] Henecka, "Chemie der β-Dicarbonylverbindungen," Springer Verlag, Berlin, 1950, p. 183.

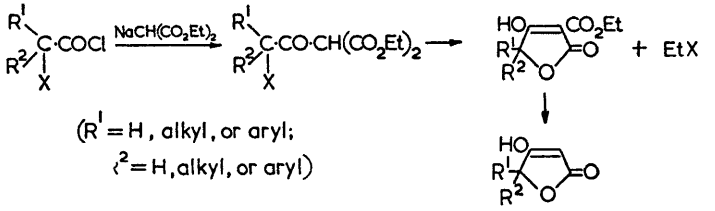
[24] See, *e.g.*, Jones, O'Sullivan, and Whiting, *J.*, 1949, 1415.

[25] Rottinger and Wenzel, *Monatsh.*, 1914, **34**, 1867.

forms is shown by the fact that γ-acetoxy-αα-dimethylacetoacetic ester can cyclise to give αα-dimethyl-β-oxobutyrolactone.[1,26]

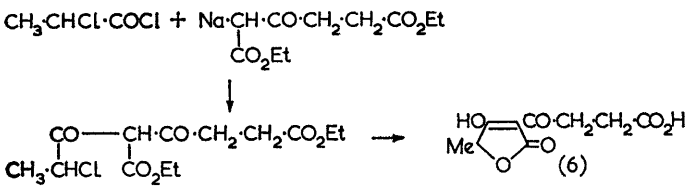
Tetronic acid itself was first prepared by Wolff[27] by sodium amalgam reduction of α-bromotetronic acid prepared by the cyclisation of αγ-dibromoacetoacetic ester. Later workers[28] have effected the reduction by catalytic hydrogenation in presence of palladium on charcoal, the double bond of tetronic acid being unaffected under the conditions employed.

Benary[29] and Anschütz[30] have given greatly increased flexibility to Demarçay's method by treating α-halogeno- or α-acetoxy-acid chlorides with sodiomalonic ester, forming γ-halogeno- or γ-acetoxy-α-ethoxycarbonylacetoacetic esters which cyclise readily to the corresponding α-ethoxycarbonyltetronic acids. These on hydrolysis and (spontaneous) decarboxylation give the corresponding tetronic acids.



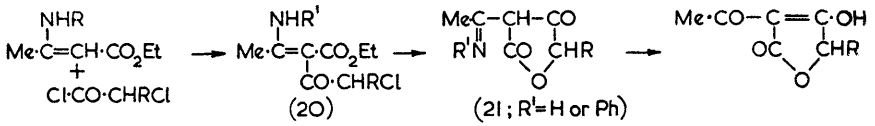
This is probably the most widely used method for the preparation of tetronic acids not substituted in the α-position. A modification using magnesiomalonic ester in place of the sodio-compound has been reported[31] to give improved yields: cyclisation of the γ-acyloxy-compounds has been shown to proceed more satisfactorily in cold 100% sulphuric acid.[32]

Benary's method can also be applied to the synthesis of α-acyltetronic acids by condensation of an α-halogenoacyl chloride with the sodio-derivative of an ethyl acetoacetate and ring closure of the product. This method was used by Haynes and Plimmer in the synthesis of (±)-carolinic acid (6).[31]



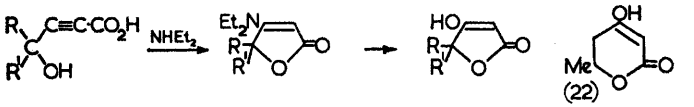
[26] Reid, Fortenbaugh, and Patterson, *J. Org. Chem.*, 1950, **15**, 572.
[27] Wolff and Schwabe, *Annalen*, 1896, **291**, 231.
[28] Reuter and Welch, *J. Proc. Roy. Soc. New South Wales*, 1939, **72**, 120.
[29] Benary, *Ber.*, 1907, **40**, 1079.
[30] Anschütz and Bertram, *Ber.*, 1903, **36**, 468; *Annalen*, 1909, **369**, 169; **368**, 23.
[31] Haynes, Plimmer, and Stanners, *J.*, 1956, 4661; Haynes and Plimmer, *Chem. and Ind.*, in the press.
[32] Reid and Denny, *J. Amer. Chem. Soc.*, 1959, **81**, 4632.

A further method for the preparation of α-acyltetronic acids is also due to Benary:[33,2] condensation of ethyl β-anilino(or β-amino)crotonate with an α-halogenoacyl chloride in presence of dry pyridine gives the derivative (20) which cyclises readily to give an acetamido-compound (21) which



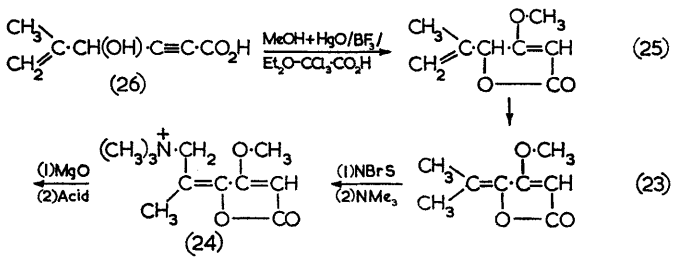
yields the α-acyltetronic acid on hydrolysis. Modifications of this reaction giving improved yields have been described by Rebstock and Sell.[17]

(2) *Hydration of αβ-acetylenic γ-hydroxy-acids.* Tetronic acids may be prepared[34,35] by the addition of secondary amines or alcohols to αβ-acetylenic γ-hydroxy-acids and subsequent hydrolysis of the products. Formation of the lactone ring is spontaneous, the addition to the triple bond giving a "*cis*"-product, *i.e.*, with the carboxyl and hydroxyl groups on the same side of the double bond. The method has been applied successfully to the preparation of six-membered ring homologues (*e.g.*, 22) of tetronic acids, and forms a convenient route to γ- and γγ-substituted tetronic acids, limited only by the availability of the αβ-acetylenic hydroxy-



acids, which are prepared by carboxylation, usually under pressure, of the Grignard reagents[35] or sodio-derivatives[36] of the acetylene carbinols.

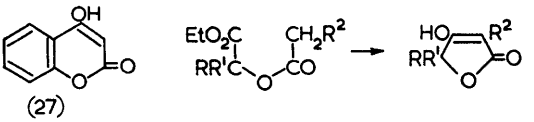
Penicillic acid (11) was synthesised by the action of *N*-bromosuccinimide on the lactone (23) and subsequent mild alkaline treatment of the quaternary salt (24) followed by acidification to give penicillic acid. The lactone (23) was obtained by rearrangement of its isomer (25) which had been



[33] Benary, *Ber.*, 1909, **42**, 3912.
[34] Jones and Whiting, *J.*, 1949, 1419, 1423.
[35] Haynes and Jones, *J.*, 1946, 503.
[36] Raphael, *J.*, 1947, 805.

prepared by addition of methanol to the triple bond of the acetylenic compound (26) under the influence of a suitable catalyst.[37]

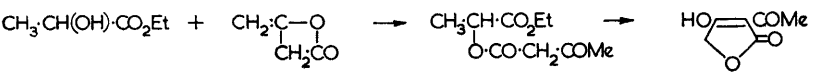
(3) *Internal Claisen ester condensation of α-acyloxy-esters.* A standard route for the preparation of 4-hydroxycoumarin (27) is cyclisation of ethyl *o*-acetoxybenzoate with sodium, an internal Claisen ester condensation taking place.[38]



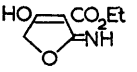
(27)

Haynes and Stanners[39] have recently reported the preparation of various tetronic acids by an analogous route from α-acetoxy- and α-phenylacetoxy-esters, and although attempts to prepare tetronic acid itself and γ-methyltetronic acid were unsuccessful, the reaction proceeded very satisfactorily with hydroxy-esters in which the hydroxyl group was tertiary, especially when di-isopropylaminomagnesium bromide was used as a condensing agent in place of sodium.

Lacey[40] has prepared several α-acetyltetronic acids by reaction of α-hydroxy-esters with diketen and subsequent ring closure of the resulting acetoacetic ester:



(4) *Miscellaneous methods of preparation.* The use of cyanoacetic ester in place of sodioacetic ester in Benary's synthesis gives rise to the product (28) which can be hydrolysed to a tetronic acid.[41]



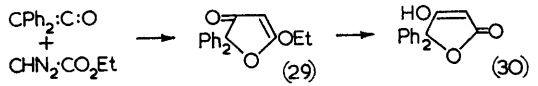
(28)

Reduction of α-acyltetronic acids to the corresponding α-alkyltetronic acids can be simply effected under the influence of a palladium on charcoal catalyst.[42]

Kende[43] has shown that reaction between diazoacetic ester and diphenyl-

[37] Raphael, *J.*, 1948, 1508.
[38] Pauly and Lockemann, *Ber.*, 1915, **48**, 28; Stahlman, Wolff, and Link, *J. Amer. Chem. Soc.*, 1943, **65**, 2285.
[39] Haynes and Stanners, *J.*, 1956, 4103.
[40] Lacey, *J.*, 1954, 832.
[41] Anschütz, *Ber.*, 1912, **45**, 2374.
[42] Clutterbuck, Raistrick, and Reuter, *Biochem. J.*, 1935, **29**, 1300.
[43] Kende, *Chem. and Ind.*, 1956, 1053.

keten gives the product (29), a type of ether which is discussed in a later section. This compound is readily hydrolysed to $\gamma\gamma$-diphenyltetronic acid (30).



Physical and chemical properties

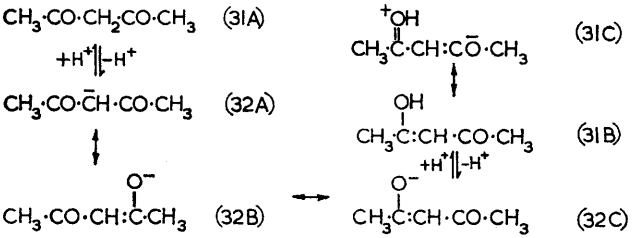
Keto-enol Equilibrium and Acidity.—A comparison of the properties of acetoacetic ester and acetylacetone provides a convenient point of departure for any discussion relating to enolisation and acidity of the tetronic acids. Table 1 shows the acidities of these two compounds in water and the

TABLE 1

	% Enol in liquid[44]	p_K*	p_E†[45]
$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO_2Et$	7·5	10·49	8·09
$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}CH_3$	80	8·94	8·13‡

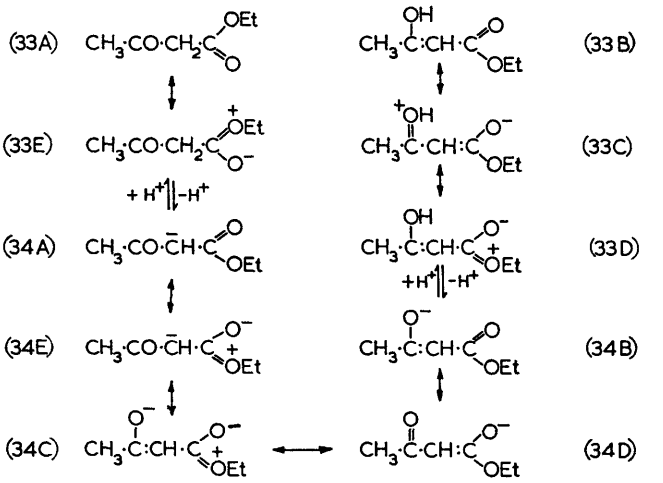
* $p_K = -\log [H^+][A^-]/[\text{Keto}]$
† $p_E = -\log [H^+][A^-]/[\text{Enol}]$
‡ Measured at 25°; other values at 30°.

percentages of enolic form in the pure liquids. It has been suggested by Ingold[46] that the difference between the effects of the ethoxycarbonyl and acetyl groups is due mainly to their conjugative (—*M*) effects which are in the order $-CO{\cdot}CH_3 > -CO_2Et$. Thus the ethoxycarbonyl group contributes little to the stabilisation of the enolic form in contrast to the acetyl group. The operation of such an effect is suggested by comparison of the heats of hydrogenation of methyl methacrylate and isobutene which



are so close as to indicate that conjugation between a C–C double bond and the ethoxycarbonyl group affords little resonance stabilisation.[47] In both cases chelation will probably have a similar effect on the stability and dissociation constant of the enolic forms.

[44] Schreck, *J. Amer. Chem. Soc.*, 1947, **71**, 1881.
[45] Schwarzenbach and Felder, *Helv. Chim. Acta*, 1944, **27**, 1044, 1701.
[46] Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell, London, 1953, p. 555.
[47] Wheland, "The Theory of Resonance," John Wiley, New York, 1944, p. 61.



The structures which may contribute to the tautomeric forms and mesomeric anions of acetylacetone and acetoacetic ester have been set out (31—34). To pass from one tautomeric form to another there must be loss of a proton followed by reattachment to the mesomeric anion. This situation has been discussed by Ingold,[48] who, from considerations of energetics, states that the less stable tautomer will be ionised more quickly and to a greater equilibrium extent than the more stable tautomer into which it may pass by way of the ionised form, which is the least stable form of the molecule.

Further consideration suggests that the small conjugative effect of ethoxycarbonyl will lower the contribution of forms (34B), (34C), and (34D) to the anion of acetoacetic ester and unfavourable charge distribution will depress the contribution of (34E), and probably also (34C); thus the anion will be less stabilised than that of acetylacetone with its three contributing forms, two of which are of equal energy and are also favoured by the $-M$ effect of acetyl.

The energy differences are reflected in the relative percentages of keto and enol forms present in the pure liquids, and also in the disparities between the two ionisation constants for keto and enol forms of acetoacetic ester and the similarities between those of keto and enol forms of acetylacetone. Although the inductive effects facilitating proton loss in the keto-forms might be expected to be similar, the free-energy changes associated with proton loss from carbon appear to differ greatly in the two, as reflected in their dissociation constants.

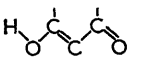
Thus the often profound effect of a slight change in constitutional factors on the thermodynamic quantities which determine the equilibrium

[48] Ref. 46, p. 566.

position of a tautomeric system frequently render such reasoning by analogy of questionable value.

The conditions determining equilibrium are greatly altered by the rigidity of a keto–enol system fused in a cyclic compound and by its inability to form internal hydrogen bonds; *e.g.*, solvent effects will be quite different in this type of system.

The factors which govern the extent of enolisation and the acid strength of cyclic β-diketones, in which both keto-groups are fused in the ring, have not yet been fully clarified. Cyclohexane-1,3-dione is fully enolised in aqueous solution and has pK_a *ca.* 5, but here enol stabilisation through hydrogen-bonded chelate forms is not possible although it has been suggested that association through a dimeric hydrogen-bonded form may be responsible.[49] The suggestion has also been made that enolisation may be ascribed to the increased resonance stabilisation in the *trans*-coplanar arrangement (35) and to decreased repulsion between oxygen atoms in a rigid cyclic system which exists in the enolic form.[50]


(35)

The increase in the amount of keto-form in non-polar solvents at extreme dilution may result from decreased dipolar interaction and a reduction of intermolecular hydrogen-bonding.

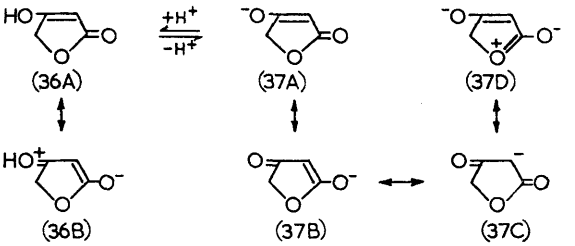
Tetronic acid in the crystalline state has been shown by spectral studies[51] to exist in the enol form. In aqueous solution Meyer titration indicates that tetronic acid is virtually 100% enol,[52] and in ethanolic solution the ultra-violet absorption points to the same conclusion.[34,53] Measurement of the dipole moment in dioxan suggests that tetronic acid is fully enolised in this solvent also.[54]

Tetronic acid itself is too insoluble in non-polar solvents to permit detailed study of the influence of solvent on keto–enol equilibrium, but from light-absorption studies Duncanson[51] has suggested that γ-methyl-tetronic acid may exist largely in the keto-form in dilute solution in methylene dichloride. Eistert,[55] using the Meyer bromine titration method, found the amount of enol form present in a benzene solution of α-methyl-tetronic acid to be 69%.

Tetronic acid is strongly acidic and has pK_a 3·76 in aqueous solution.[56] The reasons for its strongly acid nature and its stability towards alkaline

[49] Rasmussen, Brattain, and Tunnicliffe, *J. Amer. Chem. Soc.*, 1949, **71**, 1068.
[50] Hammond, "Steric Effects in Organic Chemistry," Ed. Newman, John Wiley, New York 1956, p. 450.
[51] Duncansen, *J.*, 1953, 1207.
[52] Kumler, *J. Amer. Chem. Soc.*, 1938, **60**, 857.
[53] Haynes and Plimmer, unpublished (see Plimmer, Ph.D. Thesis, Edinburgh, 1955).
[54] Kumler, *J. Amer. Chem. Soc.*, 1940, **62**, 3292.
[55] Eistert, Lecture, Hamburg, Nov., 1951, quoted by Briegleb and Strohmeier, *Angew. Chem.*, 1952, **64**, 409.
[56] Kumler, *J. Amer. Chem. Soc.*, 1938, **60**, 859.

hydrolysis have been discussed by Kumler, who considers that forms such as (37D) which carry three formal charges and contain two double bonds within the ring will, because of steric strain, contribute little to the resonance stabilisation of the anion. The anion will be stabilised to a large extent by the forms (37A) and (37B) which will be of similar energy content, and there is probably also some contribution from form (37C).



As has already been shown, the differences between acetoacetic ester and acetylacetone are accounted for, in part at least, by the much lower $-M$ effect of the carbonyl group in $-CO_2Et$ compared with that in $-CO{\cdot}CH_3$ because of the contribution of the forms $-C(O^-)=O^+Et$. If Kumler's assumption that form (37A) makes little contribution is correct, it would then follow that tetronic acid should be similar to a cyclic β-diketone. This is indeed the case. This modification of the cyclic ester grouping combined with the repulsive effect of the negative charge makes the anion of tetronic acid stable to attack by alkaline reagents under vigorous conditions. This would explain why the ethoxycarbonyl group in α-ethoxycarbonyltetronic acid is readily hydrolysed by alkali, the cyclic ester group being unaffected.

The cyclic oxygen atom will, however, exert an inductive effect through the γ-carbon atom and results in tetronic acid being a stronger acid than cyclopentane-1,3-dione (pK_a 4·5).[57] The difference in acid strengths (0·74 pK unit) is comparable to that (0·89 pK unit) between acetic acid (pK_a 4·75) and glycollic acid (pK_a 3·86).

Jones and Whiting[34] have discussed the inductive effect of the oxygen atom within the 5-membered ring and have shown that in the 6-membered ring compound (38) the additional methylene group has the expected effect of lowering the acidity (pK_a 5·15). It should be borne in mind that in


(38)

making the above comparison ring size may also influence acid strength as in the corresponding carbocyclic compounds (5,5-dimethylcyclohexane-1,3-dione, pK_a 5·15; cyclopentane-1,3-dione, pK_a 4·5).

[57] Boothe, Wilkinson, Kushner, and Williams, *J. Amer. Chem. Soc.*, 1953, **75**, 1372.

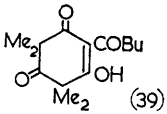
Table 2 shows the values of the dissociation constants of some substituted tetronic acids. With the exception of α-hydroxytetronic acid, the acid-weakening or -strengthening effect of groups substituted in the α-position is generally as would be predicted from their inductive effects. Insufficient data are obtainable on the strengths of γ-substituted acids to determine the effect of groups which could reinforce or compete with the inductive effect of the ring oxygen atom.

TABLE 2

Acid	pK_a	Lit. ref.
Tetronic acid	3·76 ± 0·003	56
α-Chlorotetronic acid	2·13 ± 0·013	56
α-Bromotetronic acid	2·23 ± 0·005	56
α-Iodotetronic acid	2·31 ± 0·005	56
α-Hydroxytetronic acid	4·37 ± 0·02	56
α-Nitrotetronic acid	1·68	58
α-Methyltetronic acid	4·19	59
α-Ethyltetronic acid	4·0	60
α-Benzyltetronic acid	3·69	59
α-Isopentyltetronic acid	4·16	59
αγ-Dimethyltetronic acid	4·0	60
α-Ethoxycarbonyltetronic acid	1·8	2
α-Acetyltetronic acid	1·8	2
α-Ethoxycarbonyl-γ-phenyltetronic acid	1·85	61

α-Acetyltetronic acid has been shown to be strongly internally hydrogen-bonded in the solid state and in non-hydroxylic solvents.[51] The effect of chelate hydrogen bonding is not, however, manifested in any pronounced acid-weakening effect as α-acetyltetronic acid and α-ethoxycarbonyltetronic acid are strongly acidic (pK_a 1·8).[2]

The compound (39) is only weakly acidic (pK_a 5·0 in 20% ethanol[62]), having the same order of acidity as the unsubstituted cyclohexane-1,3-diones, suggesting that the inductive effect of the carbonyl group which would be expected to increase acidity may be compensated by the acid-weakening effect of hydrogen-bonding.



(39)

The greater acid strengths of acyltetronic acids may possibly be attributed to the inductive effects of three adjacent strongly electron-attracting groups

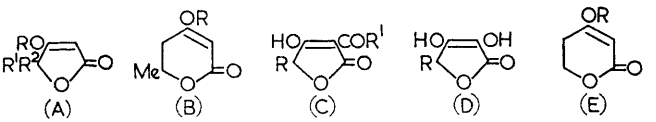
[58] Kumler, *J. Amer. Chem. Soc.*, 1942, **64**, 1948.
[59] Clarke, Haynes, and Martin, unpublished.
[60] Chopra, Cocker, Cross, Edward, and Hutchinson, *J.*, 1955, 588.
[61] Haynes and Plimmer, unpublished.
[62] Chan and Hassall, *J.*, 1956, 326.

facilitating proton loss from carbon. Russell[63] suggests that this mode of ionisation, which would involve a change in carbon co-ordination number from 4 to 3, would be strongly opposed in a 6-membered ring on steric grounds but not in the case of a 5-membered ring.

An approximate calculation based on bond-energy values suggests that a keto-form is more stable than an enol form to the extent of *ca.* 18 kcal. The keto–enol equilibrium for acetylacetone, which is 92% enol form in the vapour phase, has been discussed by Branch and Calvin who conclude that the enol form is stabilised to the extent of 19·5 kcal. over the value calculated from bond energies. They suggest that this quantity may be accounted for by addition of the partial effects: 7 kcal. for the vinyl alcohol (phenolic), 3 kcal. for the C=C—C=O system, and 8 kcal. for the hydrogen bond. The absence of this last term in the tetronic acids and other cyclic keto–enol systems suggests that the equilibrium should favour the keto-form. The fact that such systems are predominantly enolic, however, points to the presence of some factor or factors other than those quoted above which favours the enolic form: one such factor could be strong intramolecular hydrogen-bonding or solvent hydrogen-bonding. (It may be noted in this latter case that hydroxylic solvents usually reduce enolisation by satisfying the requirements of >C=O as a base. The situation in non-polar solvents where the keto-form increases may be a function of the dielectric properties of the solvent, as the more polar of the two forms will be the keto.)

It seems necessary, however, to postulate an additional factor which is associated in some way with the cyclic system in order to account for the extra stability of the cyclic enolic β-dicarbonyl system over that shown in comparable acylic systems.

Ultraviolet light absorption



Data are for ethanolic solutions unless otherwise indicated.

Compound	$\lambda_{max.}$	$\epsilon_{max.}$	Ref.
A; R = H, R^1R^2 = $[CH_2]_5$	2240	13,000	1
A; R = H, R^1 = R^2 = Me	2230	13,500	1
A; R = Me, R^1 = R^2 = Me	2180	17,000	6
A; R = H, R^1 = H, R^2 = Pr	2230	13,500	1
A; R = Me, R^1 = H, R^2 = Pr	2210	13,500	6
A; R = H, R^1 = H, R^2 = Et†	2580	12,000	2
A; R = H, R^1 = H, R^2 = Et‡	2330	12,000	2

[63] Russell, *Chem. and Ind.*, 1956, 326.

[cont. on p. 305]

Compound	$\lambda_{max.}$	$\epsilon_{max.}$	Ref.
A; R = H, R^1 = H, R^2 = Et§	2580	18,000	2
A; R = H, R^1 = H, R^2 = Et‖	2250	10,000	3
A; R = H, R^1 = H, R^2 = H (pH 1·2)	2240	14,500	4
A; R = H, R^1 = H, R^2 = H (pH 13·5)	2490	22,800	4
A; R = H, R^1 = H, R^2 = Ph (pH 1·8)	2220*	13,500	4
A; R = H, R^1 = H, R^2 = Ph (pH 12·6)	2510	21,200	4
A; R = Me, R^1R^2 = $[CH_2]_5$	2210	15,500	6
A; R = Ph, R^1R^2 = $[CH_2]_5$	2230	13,000	6
	2370*	11,000	
B; R = Me	2340	17,000	6
E; R = Me	2330	13,500	6
B; R = H	2390	12,000	1
	2420	12,000	
Me·CH:CH·C(OH):CH·CO_2H	2800	6,500	1
Me·CH:CH·C(OMe):CH·CO_2H	2650	15,000	6
MeO·CMe:CH·CO_2H	2340	13,500	5
A; R = H, R^1 = H, R^2 = Me‡	2260	15,900	2
A; R = H, R^1 = H, R^2 = Me§	2500		2
A; R = H, R^1 = H, R^2 = Me‖	2190	790	3
C; R = H, R^1 = Me†	2650	15,000	2
	2300	15,000	
C; R = H, R^1 = Me‡	2650	15,000	2
	2300	15,000	
C; R = H, R^1 = Me§	2630—2650	15,000	2
	2300	15,000	
C; R = Me, R^1 = CH_2·CH_2·CO_2H†	2650	13,800	2
	2300	12,600	
C; R = Me, R^1 = CH_2·CH_2·CO_2H‡	2650	13,800	2
	2300	12,600	
C; R = Me, R^1 = CH_2·CH_2·CO_2H§	2650	13,800	2
	2300	14,000	
C; R = Me, R^1 = CH_2·CH_2·CO_2H	2600—2650	16,800	4
	2340	15,000	
C; R = Me, R^1 = CH_2·CH_2·CO_2H¶	2500	15,000	4
D; R=H	2420	—	7
D; R = H	2460	7,400	7
D; R = HO·CH_2·CH·OH	2450	—	2
D; R = HO·CH_2·CH·OH**	2650	12,900	2

* Inflexion. † In water. ‡ In N/40-H_2SO_4. § In aqueous NaOH. ‖ In CH_2Cl_2. ¶ In ethanol containing HCl. ** In aq. acetate buffer.

[1] Jones and Whiting, *J.*, 1949, 1419. [2] Herbert and Hirst, *Biochem. J.*, 1935, **39**, 1881. [3] Duncanson, *J.*, 1953, 1207. [4] Haynes and Plimmer, unpublished (see Plimmer, Ph.D. Thesis, Edinburgh, 1955). [5] Owen, *J.*, 1945, 385. [6] Jones and Whiting, *J.*, 1949, 1423. [7] Mahler and Lohr, *Helv. Chim. Acta*, 1938, **21**, 485.

Light-absorption studies

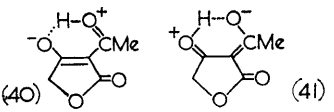
(1) *Ultraviolet.* Jones and Whiting[34] have drawn attention to the difference in light-absorption properties of tetronic acids compared with open-chain analogues or with the analogous δ-lactones (*e.g.*, 38), and comment on the unusually low wavelength of the maxima which they consider to be related to the remarkable chemical stability (see table of values).

The ultraviolet spectrum of tetronic acid[61] resembles that of a monoenolised β-diketone.[64] The light absorption in ethanol and aqueous ethanol exhibits pH dependence, and a series of curves at different pH values shows a unique isosbestic point indicating that only two species are present in solution, the enol (36A) and the enolate ion (36B). The enol has $\lambda_{max.}$ 2230 Å (log $\epsilon_{max.}$ 4·17) and the enolate ion has $\lambda_{max.}$ 2480 Å (log $\epsilon_{max.}$ 4·36) in 80% ethanol.

The structural similarity of the undissociated enols and the methyl ethers is reflected in the close $\lambda_{max.}$ and log $\epsilon_{max.}$ values.

Although the introduction of a γ-alkyl or aryl group has little influence on the maximal wavelength (γ-phenyltetronic acid as enolate ion has $\lambda_{max.}$ 2520 in aqueous solution), yet the presence of an α-alkyl group displaced the maximum to longer wavelengths by about 80 Å; *e.g.*, α-ethyltetronic acid has $\lambda_{max.}$ 2330 Å ($\epsilon_{max.}$ 12,000) and the enolate ion has $\lambda_{max.}$ 2580 Å ($\epsilon_{max.}$ 18,000).[66] This displacement is similar to that obtained by the introduction of an α-alkyl substituent into an αβ-unsaturated ketone.[67]

α-Acetyltetronic acids show absorption at 2300—2360 and 2600—2680 Å and in this respect they resemble enolised β-triketones.[66,40,68] Lacey has suggested that the bands at 2300—2360 Å are to be associated with interaction between the enol double bond and the lactone carbonyl group and that the bands at 2600—2680 Å can be attributed to the HO·C:C·CO·CH_3 chromophore. It would follow in the latter case that exaltation of the absorption band must be due partly to the auxochromic effect of the OH substituent but is chiefly due to the increased resonance arising from intramolecular hydrogen-bonding as in (40) and (41).



(40) (41)

In view of this suggestion it might be expected that on ionisation there would be a change in absorption maximum on passing from the non-ionised hydrogen-bonded form to the ionic form, but Herbert and Hirst[66] found that there was no change in intensities or absorption maxima of the

[64] Cf. Meek, Turnbull, and Wilson, *J.*, 1953, 2891.
[66] Herbert and Hirst, *Biochem. J.*, 1935, **29**, 1881.
[67] Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 76.
[68] Birch and Todd, *J.*, 1952, 3102.

two bands of α-acetyltetronic acid when measurements were made in water, acid (N/40-H_2SO_4), or alkali (N/50-NaOH). It has already been mentioned that the acid-weakening effects of hydrogen-bonding are not manifest to any great extent in this compound (see previous section).

In spite of the similarities in position and intensities of the absorption maxima, the behaviour in methanolic solutions of acetyltetronic acids on change of pH differs from that of the acylcyclohexane-1,3-diones. A study of 2-isovaleryl-4,4,6,6-tetramethylcyclohexane-1,3,5-trione at different pH values shows that there is a decrease in intensity of the peak at 2380 Å and a large increase in intensity of that at 2790 Å as the pH is increased.[62]

In ethanol or ethanol acidified with hydrochloric acid, acetylcyclohexane-1,3-dione displays the two characteristic bands at 2310 and 2760 Å,[62] whereas tetronic acids possessing an α-carbonyl group have been shown to display unusual behaviour in acidified ethanol: the absorption band at lower wavelengths disappears and the band in the 2600 Å region undergoes a change in wavelength. The shift in carolinic acid is from 2600 to 2500 Å, and in α-acetyl-γ-phenyltetronic acid from 2640 to 2690 Å.[61]

The ultraviolet absorption spectra of simple tetronic acids is consistent with their other chemical and physical properties, but the α-acetyltetronic acids show marked differences in spectral behaviour from α-acylcyclohexanediones to which they are formally analogous. The reasons for these differences are not clear and merit further investigation.

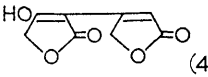
(2) *Infrared.* The infrared spectra of tetronic acids have been studied by several workers. Duncanson[51] draws the following conclusions from an examination of the spectra in the solid state and in solution: (i) Alkyltetronic acids exist in the solid state as enol forms associated through strong intermolecular hydrogen bonds, which give rise to OH bands in the region 2500—2700 cm.$^{-1}$, and the carbonyl frequencies are much lower than would be expected for a 5-membered ring lactone. Double-bond stretching bands are observed in the 1650—1700 cm.$^{-1}$ and the 1565—1580 cm.$^{-1}$ region. (ii) In chloroform solution double-bond frequencies are shifted to higher wavelengths, appearing at 1740 and 1630 cm.$^{-1}$ (1740 and 1675 cm.$^{-1}$ for α-substituted acids), which is consistent with the change from the associated form to the monomer. (iii) In ethylene dichloride solution γ-alkyltetronic acids display bands at 1800 and 1760 cm.$^{-1}$, which are indicative of a saturated 5-membered lactone ring and a 5-membered cyclic ketone respectively, leading to the conclusion that the keto-form predominates in this solvent. (iv) α-Acetyltetronic acids show a band at 1758 cm.$^{-1}$ which is that of an αβ-unsaturated lactone carbonyl group unmodified by hydrogen-bonding. There is no major change in the spectrum in passing from solid state to solution which is consistent with the intramolecular hydrogen-bonded form proposed. (v) Methyl ethers display normal lactone and double-bond frequencies (1735 and 1628 cm.$^{-1}$ respectively).

These conclusions are borne out by later studies on a wide range of

tetronic acid derivatives. Haynes and Jamieson[69] found the OH absorption bands relatively weak and extremely broad, and used the shift obtained by deuteration to obtain information concerning this region. Deuterated alkyltetronic acids showed strong absorption in the 2100—2200 cm.$^{-1}$ region, which indicates that the OH bands occur at about 2900 cm.$^{-1}$—the region for enolic β-diketones which have intramolecular bonding—and it is suggested that this OH absorption is of the conjugated chelate type as in dimedone.[49] Direct intramolecular hydrogen bonds would be prohibited by steric considerations.

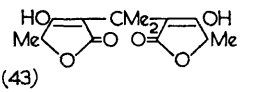
Reactions of tetronic acids

(1) *Anhydrotetronic Acid.* This acid was first obtained by Wolff and Schwabe[27] by heating an aqueous solution of tetronic acid. The compound separates with one molecule of water of crystallisation and evidence has been presented[70] to show that it possesses structure (42). Anhydro-


(42)

tetronic acid is mono-enolic, and like tetronic acid, gives a colour with ferric chloride and couples with diazonium compounds. It is a stronger acid (pK 1·99) than tetronic acid. It has not been possible to prepare corresponding anhydro-acids from γ-substituted tetronic acids, as might be expected if anhydrotetronic acid has the structure (42), and it has been suggested that steric factors may govern the course of the reaction.

Tetronic acids condense with aldehydes, ketones, or ketonic acids,[71] and a description[5] has been given of the isolation of products from *P. Charlesii* G. Smith, which it was later realised were artefacts[42] produced by condensation of γ-methyltetronic acid with acetone. The condensation proceeds readily, even in dilute aqueous solution, in 2—3 hours, especially in presence of dilute hydrochloric acid, or on boiling for a few minutes in ethanol, to give isopropylidene-bis-γ-methyltetronic acid (43). Further condensation with a second molecule of acetone gives (44) and a compound, possibly (45), may also be obtained.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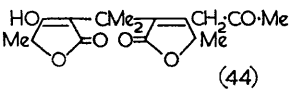
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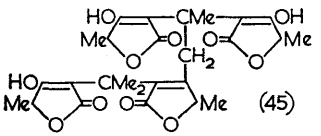
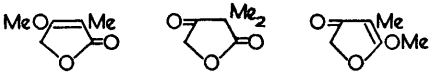

(45)

[69] See Jamieson, Ph.D. Thesis, Edinburgh, 1957.
[70] Marrian, Russell, Todd, and Waring, *J.*, 1947, 1365.
[71] Wolff, *Annalen*, 1901, **315**, 145; Wolff and Schlimpf, *ibid.*, p. 151.

(2) *Alkylation.* Recent studies of the methylation of α-methyltetronic acid have shown that three different products can be formed.[72] Treatment of the sodium salt of a tetronic acid with dimethyl sulphate in sodium hydroxide gives the *O*-methyl ether (A) as the sole product, but alkylation of the silver salt of α-methyltetronic acid with alkyl iodide in benzene



(A) (B) (C)

gives two liquid products, one the expected *O*-methyl ether, the other the *C*-methyl derivative (B). *C*-Alkylation in this fashion has not previously been reported with tetronic acid derivatives although it is not an unexpected reaction. Methylation of α-methyltetronic acid with diazomethane in ether gives the normal *O*-methyl ether (A), together with a crystalline isomeric substance which is readily hydrolysed by water to give α-methyltetronic acid. This new ether was at first thought to be a crystalline sample of (A), and since the methylation product of zymonic acid (see p. 294) was quite different in its ultraviolet absorption and stability to hydrolysis, it was thought that zymonic acid was not a tetronic acid derivative. However, the properties of methylated zymonic acid are closely similar to those of the liquid methyl ether (A), the structure of which is beyond dispute. It follows that zymonic acid is the tetronic acid derivative (45). The properties of the new crystalline methylation product and its ultraviolet and infrared absorption spectra show it to have structure (C). Analogous structures have been demonstrated for the diazomethane methylation products of 6-methyl- and 6-phenyl-pyrone and 4-hydroxycoumarin.[73,74]

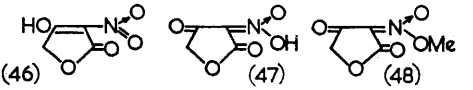
(3) *Acylation.* Tetronic acids[75] have recently been shown to be acylated in the α-position under Friedel–Crafts conditions. Stannic and zinc chlorides are better as catalysts than aluminium chloride, and the reaction provides a useful preparative route to the preparation of α-acyl-γγ-disubstituted tetronic acids. It has also been shown that γ-substituted tetronic acid acetates can be rearranged under the conditions for the Fries rearrangement of phenolic esters to give α-acyltetronic acids.

The Friedel–Crafts-type acylation presumably involves an electrophilic acylium-ion attack on the tetronic acid nucleus: the Fries type rearrangement may be formulated as indicated by Baltzly.[76]

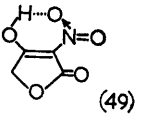
(4) *Nitration, nitrosation, and coupling.* On treatment with concentrated nitric acid at 0° tetronic acid yields α-nitrotetronic acid,[77] a

[72] Haynes, Jamieson, and Stanners, unpublished; see Jamieson, Ph.D. Thesis, Edinburgh, 1957; Stanners, Ph.D. Thesis, Edinburgh, 1956.
[73] Chmielewska and Cieslak, *Przemysl Chem.*, 1952, **8**, 196; Janiszewska-Drabarek, *Roczniki Chem.*. 1953, **27**, 456.
[74] Herbst, Mors, and Djerassi, *J. Amer. Chem. Soc.*, 1959, **81**, 2427.
[75] Haynes and Jamieson, *J.*, 1958, 4132.
[76] Baltzly, Ide, and Phillips, *J. Amer. Chem. Soc.*, 1955, **77**, 2522.
[77] Wolff and Lüttringhaus, *Annalen*, 1900, **312**, 133.

strong acid (pK_a 1·68).[58] Two possibilities (46) and (47) must be considered for the structure of this product. There seems little doubt that the methyl ether of α-nitrotetronic acid has the formula (48) since it readily forms an oxime. The free acid will also form an oxime and a phenyl-



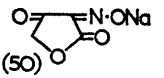
hydrazone and gives no colour with ferric chloride, and this evidence was taken by Wolff and Lüttringhaus as suggesting that the acid had structure (47): however, Kumler has pointed out that *o*-nitrophenol does not give a colour with ferric chloride and suggests that the dissociation constant and dipole moment are consistent with structure (46) in which strong hydrogen bonding occurs [formulated in (49)].



The high melting point (184°, decomp.) suggests that there is a considerable intermolecular hydrogen bonding in solid α-nitrotetronic acid: the acid is easily soluble in water and alcohol and only sparingly soluble in non-polar solvents and, as already mentioned, is a strong acid. This suggests that the intramolecular hydrogen-bonded structure is the less likely: clearly, spectral evidence would be of value in deciding between these two possible structures.

Reduction of α-nitrotetronic acid with sodium amalgam or with zinc and acid gives α-aminotetronic acid.[27]

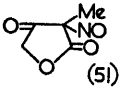
Tetronic acids which are unsubstituted in the α-position give a purple colour on treatment with sodium nitrite because of the formation of sodium salts of the hydroxyiminotetronic acids (50). Acidification of the sodium salt of hydroxyiminotetronic acid gives the free acid as yellow leaflets,



easily soluble in water and alcohol. On treatment with dilute nitric acid it forms α-nitrotetronic acid: with hydroxylamine it forms an oxime.[27] Here again spectral studies would be of considerable interest in establishing the structure of the nitroso-compound.

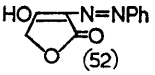
Treatment of α-methyltetronic acid with dinitrogen trioxide (from arsenious oxide and nitric acid) gives the corresponding α-nitroso-

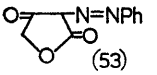
compound (51) as a neutral solid which when boiled with water gives α-methyltetronic acid, nitrous acid, and some α-hydroxyiminopropionic acid.[78]

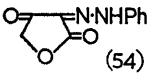

(51)

Treatment of the α-nitroso-compound with nitric acid gives a compound, $C_5H_5O_6N$, which is also formed similarly from α-methyltetronic acid. The structure of this compound is unknown; it contains one more oxygen atom than the corresponding α-nitro-compound: on hydrolysis it forms biacetyl, hydrogen cyanide, carbon dioxide, and nitric acid, and it readily oxidises potassium iodide and ferrous salts. Similarly, a compound, $C_6H_7O_6N$, is formed from α-ethyltetronic acid.[79]

Tetronic acid couples with benzenediazonium chloride in alkaline solution to give a golden-yellow product.[77] The structure of this may be (52), (53), or (54); of these, Wolff favoured (54) since the compound gave

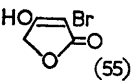

(52)


(53)


(54)

no colour with ferric chloride and readily formed an oxime and a phenylhydrazone. α-Methyltetronic acid couples with benzenediazomium chloride but the initial product is unstable and the product isolated is the phenylhydrazone of pyruvoylacetic acid, $NHPh{\cdot}N{=}CMe{\cdot}CO{\cdot}O{\cdot}CH_2{\cdot}CO_2H$, which suggests that the product from tetronic acid could not have structure (53). The coupling product dissolves in alkali, and Wolff has suggested that the sodium salt is derived from structure (52).

(5) *Halogenation.* Tetronic acids with a free α-position on treatment with bromine in dry chloroform yield the corresponding monobromotetronic acids (55).[27] These are strong acids: the bromine atom is not


(55)

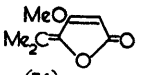
readily replaced by hydrolysis. Micheel and Jung[80] attempted to prepare α-hydroxytetronic acid by treatment of α-bromotetronic acid with sodium hydroxide for some hours and stated that hydroxytetronic acid is formed but cannot be isolated in a pure form. Treatment of α-bromotetronic acid with sodium nitrite gives a purple colour due to formation of the sodium salt of α-hydroxyiminotetronic acid: with dry hydrogen chloride in dry ethanol the bromine is replaced by chlorine, giving α-chlorotetronic

[78] Wolff, *Annalen*, 1895, **288**, 1.
[79] Wolff, *Annalen*, 1913, **399**, 309.
[80] Micheel and Jung, *Ber.*, 1933, **66**, 1291.

acid.[81] Reduction of the bromo-compound with sodium amalgam[27] or, better, by catalytic hydrogenation[28] gives tetronic acid.

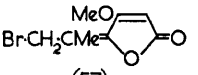
Treatment of tetronic acid with iodine gives α-iodotetronic acid which will oxidise iodide quantitatively to iodine in acid solution (*i.e.*, the reaction is reversible).[82]

Raphael[37] has shown that direct bromination in acetic acid of the tetronic acid methyl ether (56) yields the expected α-bromo-derivative;



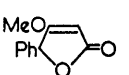
(56)

N-bromosuccinimide yields the compound (57).

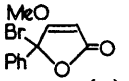


(57)

Nineham and Raphael[13] have shown, however, that the tetronic acid methyl ether (58) on treatment with bromine in carbon tetrachloride



(58)



(59)

yields the γ-bromo-derivative (59) in which the bromine is easily replaced by hydroxyl.

(6) *Sulphonation.* Treatment of tetronic acid with fuming sulphuric acid gives the corresponding α-sulphonic acid derivative,[82] which is very soluble in polar solvents, less so in benzene and ether, and is somewhat unexpectedly reported as neutral.

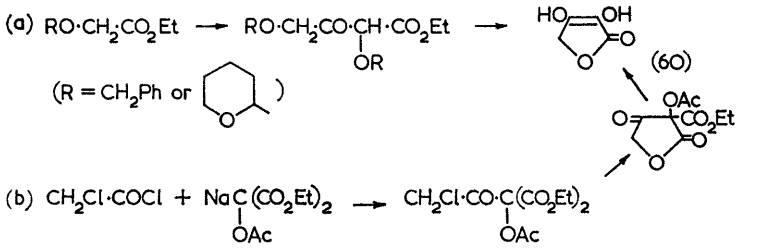
Tetronic acids then readily enter into electrophilic substitution reactions, and in their modes of reaction and reactivities resemble phenols possessing solely a free *ortho*-position. The nucleus is not readily disrupted. These properties are explicable on the basis of the electronic structures of the tetronic acids discussed in the preceding section.

Preparation and properties of substituted tetronic acids

(1) *α-Hydroxytetronic Acids.*—It has already been noted that vitamin C is a γ-substituted hydroxytetronic acid and some of the methods used for the synthesis of this and related compounds are modifications of more generally applicable syntheses.[83]

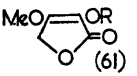
[81] Kumler, *J. Amer. Chem. Soc.*, 1938, **60**, 857.
[82] Wolff and Fertig, *Annalen*, 1900, **312**, 164; see also **Ref. 81.**
[83] Smith, *Adv. Carbohydrate Chemistry*, 1942, **2**, 79.

α-Hydroxytetronic acid (60) has been prepared in an impure state by hydrolysis of α-bromotetronic acid,[80] and it has also been obtained by a Claisen ester condensation of the benzyl[80] or tetrahydropyranyl ether of glycollic ester and subsequent hydrolysis (scheme a).[84]



Benary's method has also been adapted to the synthesis of α-hydroxytetronic acid by condensation of the sodio-derivative of acetoxymalonic ester with chloroacetyl chloride and subsequent ring closure with hydrolysis and decarboxylation of the α-ethoxycarbonyl group (scheme b).[85]

α-Hydroxytetronic acid melts at 153°. It possesses two enolic hydroxyl groups, one of which can be titrated with alkali (phenolphthalein). Like ascorbic acid, it is readily oxidised, especially by iodine or in presence of a trace of copper, yielding one αβ-diketo-γ-butyrolactone.[86] Micheel and his co-workers[86,87] have studied the methylation of hydroxytetronic acid with diazomethane. The first product is the 3-methyl ether (61; R=H);



(61)

further methylation gives the 2,3-dimethyl ether (61; R=Me) as a neutral liquid. Hydrolysis of this product with alkali first opens the lactone ring and then yields α-methoxytetronic acid.[87] These properties are consistent with the expected stronger acid character of the 3-hydroxyl group.

In spite of the resemblance to vitamin C, α-hydroxytetronic acid possesses no antiscorbutic activity[88] and its presence in foods interferes with quantitative determinations of the vitamin based on the reactions of the ene–diol system, *e.g.*, reduction of dichlorophenol-indophenol blue. Separation of the two compounds has been achieved by paper chromatography.[89]

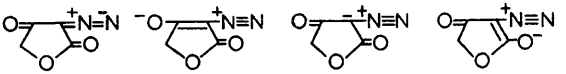
(2) *α-Aminotetronic Acids.*—α-Aminotetronic acid was originally prepared by reduction of α-nitrotetronic acid by tin or zinc in acid or with sodium amalgam.[77] The diazo-compound prepared by the action of

[84] Haynes and Plimmer, *J.*, 1956, 4665.
[85] Ghose, *J. Indian Chem. Soc.*, 1946, **23**, 311.
[86] Micheel and Jung, *Ber.*, 1934, **67**, 1660.
[87] Micheel and Schulte, *Annalen*, 1935, **519**, 70.
[88] Dalmer and Moll, *Z. physiol. Chem.*, 1933, **222**, 116.
[89] Mapson and Partridge, *Nature*, 1949, **164**, 479.

benzenediazonium chloride on a tetronic acid can also be reduced in the presence of a palladium catalyst to the corresponding amino-compound.[90]

α-Aminotetronic acid forms colourless needles of high melting point and, like α-hydroxytetronic acid, it is readily oxidised.

Reaction of aminotetronic acids with nitrous acid gives rise to diazo-compounds[77,91] which resemble diazotised *o*-aminophenol in their chemical behaviour and should probably be formulated in a similar manner as resonance hybrids of the structures (62, *a*—*d*). Diazotetronic acids are



(62)

not so reactive as simple aromatic diazo-compounds, and comparison can be made with the stable "diazo-anhydrides" of the aliphatic series, *e.g.*, $R{\cdot}CO{\cdot}CN_2{\cdot}CO_2Et$, where the adjacent carbonyl groups have a similar stabilising effect on the diazo-group.[92]

(3) *α-Acyltetronic Acids.*—The preparation of these compounds has already been discussed. It is noteworthy, however, that attempts so far described to acylate an organometallic derivative of tetronic acid have proved unsuccessful, although Reuter and Welch[28] possibly obtained α-acetyl-α-ethoxycarbonyltetronic acid by the action of acetyl chloride on the sodio-derivative of α-ethoxycarbonyltetronic acid: in view of the results obtained in alkylation of the silver salt of α-methyltetronic acid (see p. 309) it would be of interest to re-examine this approach.

α-Acetyltetronic acid is strongly acidic (pK_a 1·8). The reactivity of the methyl group of the acetyl is diminished and condensation with an aldehyde gives only a poor yield of the corresponding unsaturated derivative.[2] Normal carbonyl derivatives of the acyl group are readily prepared. Hydrogenation of α-acetyltetronic acid with a palladium–carbon catalyst yields α-ethyltetronic acid;[42] under similar conditions dehydracetic acid yields 3-ethyl-6-methylpyrone.[93]

With diazomethane α-acyltetronic acids yield methyl ethers[94] in contrast to 2-acetylcyclohexane-1,3-dione which is reported as being inert towards this reagent.[95]

The α-acetyltetronic acids are unaffected by boiling sodium hydroxide solution, and Lacey[40] has reported that α-acetylspirocyclohexyltetronic acid is stable to boiling concentrated hydrochloric acid or 80% sulphuric acid at 100°.

[90] Lecocq, *Compt. rend.*, 1951, **18**, 183.
[91] Pons and Veldstra, *Rec. Trav. chim.*, 1955, **74**, 1217; see also Weygand, Bestmann, and Fritsche, *Z. Naturforsch.*, 1957, **12***b*, 597.
[92] Wolff, *Annalen*, 1903, **325**, 129.
[93] Berson, *J. Amer. Chem. Soc.*, 1952, **74**, 5772.
[94] Clutterbuck, Raistrick, and Reuter, *Biochem. J.*, 1935, **29**, 871.
[95] Smith, *J.*, 1953, 803.

α-*Alkoxycarbonyltetronic Acids.*—α-Alkoxycarbonyltetronic acids are intermediates in Anschütz and Benary's methods for the preparation of tetronic acids. They are readily hydrolysed in alkali to the salts of the corresponding carboxylic acids, but the acids themselves are decarboxylated spontaneously. The reaction is interesting in emphasising the resistance of the tetronic acid nucleus to alkaline hydrolysis.