STUDIES IN THE TETRONIC ACIDS

by

John W. McK. Jamieson, B.Sc., A.R.I.C.

Thesis submitted for the degree of DOCTOR OF PHILOSOPHY

TO MY MOTHER
SUMMARY

A short account is given of the natural occurrence of tetronic acid derivatives, the general characteristics of the tetronic acids are mentioned, and the methods available for synthesising the acids are indicated. An improved method of preparing \( \gamma \)-methyItetronic acid is described.

The ethers of some tetronic acids were prepared by means of diazomethane, dimethyl sulphate and alkyl halides. \( \gamma \)-Phenyl- and \( \gamma \gamma \)-diphenyltetronic acids when treated with diazomethane were found to give only the ethers of their normal enolic forms, although \( \alpha \)-methyItetronic acid gives a second solid ether also. The keton-acetal structure suggested by A. H. Stanners (Ph. D. Thesis, Edin. 1955, p.23) for the solid methyl ether of \( \alpha \)-methyItetronic acid is shown to agree with its I.R. absorption spectrum.

The sodium salts of some tetronic acids in polar solvents on treatment with alkyl halides or dimethyl sulphate were found to give the normal ethers. These ethers showed varying degrees of stability to alkali, the ether link being rather more susceptible than the lactone ring to alkaline hydrolysis.

Treatment of silver \( \alpha \)-methyItetronate with methyl iodide in boiling benzene was confirmed to give mainly
G-alkylation (first reported by A. H. Stanners, op. cit., p. 21) by comparing the derivatives and I.R. absorption spectrum of the product with those of authentic \( \alpha, \beta \)-dimethyl-\( \gamma \)-oxobutyrolactone. Similar experiments using ethyl and \( \beta \)-butyl iodides showed that the proportion of O-alkylation to C-alkylation is directly dependent upon the hyperconjugation associated with the alkyl halide, in accordance with the theory of Kornblum (J. Amer. Chem. Soc., 1955, 77, 6269).

An attempt is made to correlate these results. The I.R. absorption spectra of some neutral tetronic acid derivatives are tabulated and considered briefly.

An investigation into the phenolic properties of the tetronic acids is described, including attempts at Fries and Claisen rearrangements and Friedel-Crafts and Hoesch reactions. The currently accepted mechanisms for these reactions are described. \( \gamma \)-Phenyltetronic acid was used in preliminary investigations; authentic \( \alpha \)-acetyl-\( \gamma \)-phenyltetronic acid was obtained by two new adaptations of existing methods.

Three \( \alpha \)-acetyl-tetronic acids were prepared by means of both Fries and Friedel-Crafts reactions, and the first \( \alpha \)-benzoyl and \( \alpha \)-allyl derivatives of tetronic acids to be reported were obtained by rearrangements. An attempt to
prepare authentic α-allyl-γ-phenyltetronic acid by C-alkylation of potassium γ-phenyltetronate with allyl bromide (successful with β-diketones; Stetter and Diericks, Ber., 1952, 85, 61) was unsuccessful, but resulted in α-hydroxy-γ-phenyltetronic acid, an analogue of ascorbic acid.

The anomalous properties of tetronic acid, and the extent to which the tetronic acids compare with the phenols, are discussed. The phenolic properties of the tetronic acid nucleus emphasise the fact that a continuous cyclic molecular orbital of the accepted kind is not necessary for the possession of considerable "aromatic" properties.

The I.R. absorption spectra of free tetronic acids and of α-acyltetronic acids are tabulated and contrasted. Conclusions are drawn relating to hydrogen-bonding.
GENERAL INTRODUCTION

Natural Occurrence.

Tetronic acids have been isolated from many natural sources. Pulvinic (I) and vulpinic (II) acids are components of the colouring matter of lichens of the families Cypheliaceae, Parmeliaceae and Hystemaceae. Ascorbic acid (III) (Vitamin C) is wide-spread, being present in the juice of citrus fruits and in green vegetables generally, and it has also been identified as a product of mould metabolism.

From cultures of Penicillium charlesii, a mould obtained from spoiled Italian maize, a series of tetronic acids have been obtained and identified (IV - VIII) while terrestrial (IX) and penicillic (X) acids have been isolated from P. terrestre and P. nuberculm respectively. Another unsaturated lactonic acid, zymonic acid, produced when the yeasts Trichosporon capitatum, Hansenula subpelliculosa and Kloeckera brevis are grown in aerated culture on a medium containing glucose, also has a tetronic acid structure (XI) (A. H. Stanners, Ph. D. Thesis, Edin. 1956, p.16). This is discussed further in the present work.

Finally, anhydrotetronic acid is one of the few synthetic compounds which are active in hatching cellworm larvae.

Of these naturally occurring compounds only γ-methyltetronic, ascorbic, penicillic and carolinic acids have been synthesised.
IV $R = H$, $(-)-\delta$-methyldtetronic acid.

V $R = COCH_2CH_2CH_2OH$, carolic acid (hydrated).

VI $R = COCH_2CH_2CO_2H$, carolinic acid.

VII $R = COCH_2CH_2CH_3$, carolsic acid.

IX $R = COCH_2CH_2CHOH\cdot CH_2CH_3$ (hydrated).

X $R = COCH_2CH_2\cdot CH_2CH_3$ (hydrated).
Characteristics.

Tetronic acid itself is the lactone of γ-hydroxyacetoacetic acid. It is a water-soluble crystalline solid, m.p. 141°, which is strongly acidic (pKₐ 3.76) and forms stable salts (Kumler, J. Amer. Chem. Soc., 1939, 60, 859) and gives a red colour with ferric chloride solution typical of an enolic system. From what presumably is its ketonic form (II) it gives a phenylhydrazone and an oxime. Tetronic acid is unexpectedly stable and no degradation or opening of the lactone ring occurs on boiling with sodium hydroxide solution.

The properties of the parent unsubstituted tetronic acid, then, indicate that it exists in a keto-enol equilibrium in which the enol form (I) predominates in the solid state and in polar solvents and so has been investigated more extensively.

\[
\text{I} \quad \leftrightarrow \quad \text{II}
\]

A number of tetronic acids have been prepared with substituent groups in the α- or γ-position, and the properties mentioned for the parent unsubstituted acid are found to be common to all the series. All except αα-disubstituted tetronic acids are strongly acidic owing to the ionisation of a proton from the enolic hydroxyl group. This acidity is unexpected as it is not possessed by the derivatives of ethyl acetoacetate to which the tetronic acids correspond as internal esters. Acetyl and benzoyl derivatives and others of the
enolic forms are readily prepared, while oximes and phenylhydrazones have been obtained, sometimes only with difficulty, from many tetronic acids in their ketonic forms.

All the tetronic acids, too, are stable to alkali reacting to give the enolate salt only as opposed to the ready ring-opening of normal lactones.

Other Reactions.

The remarkable stability of tetronic acids is further emphasised by their tendency to undergo chemical reactions characteristic of an aromatic nucleus. Thus nitration, sulphonation and halogenation take place at the \( \alpha \)-position just as electrophilic substitution occurs in the \( \sigma \)-position in phenols. Nitrosation followed by chromic acid oxidation also gives the \( \alpha \)-nitrotetronic acid, which does not react with ferric chloride although \( p_K_a \) and dipole measurements indicate it to be enolic. \( \alpha \)-Aminotetronic acid undergoes diazotisation, and benzenediazonium chloride couples with tetronic acid.

A section of this work will be devoted to a more detailed investigation of some of the aromatic properties.

Tetronic acids which are unsubstituted in the \( \alpha \)-position give transient blue colours with sodium nitrite solution due to the formation of derivatives of \( \alpha \)-oximidotetronic acid (I) which gives purple salts with alkali metals (Wolff and Schwabe, Ann., 1896, 221, 226). This property is shown also by the \( \alpha \)-monobromotetronic acids, in which the bromine atom is readily displaced by this reagent.
When a concentrated aqueous solution of tetronic acid is heated and left to stand anhydrotetronic acid, m.p. 263° (d), separates (idem, ibid.). It is a much stronger acid (pKₐ 1.99) than tetronic acid (pKₐ 3.76) owing possibly to increased resonance. It may also be prepared by heating tetronic acid in N-methylmorpholine (Marrian, Russell and Todd, J., 1947, 1365). Its constitution has been shown to be II, arising by condensation of two molecules of tetronic acid with elimination of water. In spite of this formulation, however, no γ-substituted tetronic acids will condense in the same manner to give anhydrotetronic acid.

Two molecules of tetronic acid condense at room temperature with one molecule of a carbonyl compound to give alkylidene bis-tetronic acids (Wolff and Schlimpff, Ann., 1901, 315, 151). With acetone, for example, isopropylidene-bis-tetronic acid (III) is formed.

Acetyltetronic acid possesses a triketo system and is strongly acidic (Baker, Grice and Jansen, J., 1945, 241). The reactivity of the -CH₃ group in the -CO.CH₃ group is diminished and condensation with an aldehyde gives only a poor yield of the corresponding unsaturated derivative (IV) (idem, ibid.) but the usual derivatives of the acetyl carbonyl group can be prepared without difficulty. Reduction of the compound with
palladium on charcoal gives α-ethyltetronic acid (Glutterbuck, Raistrick and Reuter, Biochem. J., 1935, 29, 300). This reaction must involve hydrogenolysis as a second stage which emphasises the stability to reduction of the tetronic acid nucleus. Dehydracetic acid (V) which bears a formal resemblance to α-acetyltetronic acid can similarly be reduced to 3-ethyl-6-methylpyrone (Berson, J. Amer. Chem. Soc., 1952, 74, 5172).

Oxidation of tetronic acids by chromic acid gives α-diketones before hydrolysis of the lactone ring occurs (Reid, Fortenbaugh and Paterson, J. Org. Chem., 1950, 15, 572) subject to three conditions:

1. Enolisation must be possible, i.e. the α-position must not be disubstituted.
2. If the α-position is unsubstituted then the γ-position must bear only one substituent.
3. If the α-position is monosubstituted then a diketone is produced regardless of substituents at the γ-position.

The differences in behaviour Reid et al. attribute to the different resonance stabilisation of the oxidation intermediates which may or may not form α-hydroxy-compounds before decarboxylation occurs.

W. Cocker and co-workers (J., 1955, 588) have found that
a positive iodoform reaction is given by \(\alpha\)-methyl- and \(\alpha\gamma\)-dimethyltetronic acids.

The \(\alpha\)-acetyl-tetronic acids retain to widely different extents the stability to alkaline hydrolysis of the tetronic acids (Lacey, J., 1954, 532). \(\alpha\)-Acetyl-\(\gamma\)-phenyl- and \(\alpha\)-acetyl-\(\gamma\gamma\)-dimethyltetronic acids suffer complete breakdown; \(\gamma\)-methyl- and \(\gamma\gamma\)-diphenyltetronic acids are obtained by alkaline hydrolysis of their \(\alpha\)-acetyl derivatives; and \(\alpha\)-acetyl-\(\gamma\)-spirocyclohexyl- (VI) and \(\alpha\)-acetyl-\(\gamma\)-benzyl-\(\gamma\)-methyltetronic acids are completely resistant. Compound VI, indeed, is stable in boiling concentrated hydrochloric acid or in 80% sulphuric acid at 100°.
I. THE SYNTHESIS OF TETRONIC ACIDS.

Two methods of approach have been used in the synthesis of tetronic acid derivatives. The method of longer standing starts from $\beta$-keto-esters, which are induced to cyclise to form a lactone ring. The second route employs as starting materials compounds with potential lactone groups already formed.

In the first route, cyclisation may be induced by brominating or acetoxy-lating the $\beta$-keto-ester in the $\gamma$-position and allowing the product to stand, or heating it, when ethyl bromide (Demarçay, Bull. Soc. chim. France, 1880, (II), 33, 516; 34, 31) or ethyl acetate (Conrad and Cast, Ber., 1898, 31, 2726, 2954) is eliminated and the lactone ring is formed.

\[ \text{e.g. } \text{BrCH}_2\text{CO.CHMe.COEt} \rightarrow \]

Unfortunately such cyclisations occur only when an $\alpha$-substituent (electron attracting or repelling) is present in the $\beta$-keto-ester (Reuter and Welch, J. Proc. Roy. Soc. N.S.W., 1939, 72, 120) so that this route is in practice limited to the preparation of $\alpha$-alkyltetronic acids.

However, Anschütz et al. (Ber., 1903, 36, 468; Ann., 1909, 368, 53) and Benary (Ber., 1907, 40, 1079; 1911, ibid., 1759) provided a route to $\alpha$-unsubstituted tetronic acids when they found that an $\alpha$-ethoxycarbonyl group is as effective as an $\alpha$-alkyl group in promoting cyclisation of the $\beta$-keto-esters,
and can readily be removed afterwards. Such keto-esters they prepared by condensing an α-acetoxyl or α-halogeno-acyl chloride with sodiomalonate ester.

\[
\begin{align*}
\text{CH}_2\text{COCl} & \quad + \quad \text{NaCH}_2\text{COOEt} \\
\text{O.CO.CH}_3 & \quad \text{COOEt} \\
& \rightarrow \quad \text{CH}_2\text{CO.CH.COEt}
\end{align*}
\]


The second method of synthesis of tetronic acids employs a ready-made potential lactone group and cyclisation elsewhere in the molecule by means of an internal Claisen condensation. The method has been used to prepare 4-hydroxy-coumarin from ethyl α-acetoxybenzoate (Pauly and Lockemann, *Ber.*, 1943, 48, 28; Stahmann, Wolff and Link, *J. Amer. Chem. Soc.*, 1943, 65, 2285).
Using this type of reaction Lacey (J., 1954, 832) has obtained good yields of \( \alpha \)-acetyl tetronic acids from the acetoacetates of \( \alpha \)-hydroxy esters which he obtained by treatment of the hydroxy esters with diketen.

\[
\begin{align*}
\text{EtOOC} & \quad \text{CH}_2\text{Ac} \\
R'R'' & \quad \text{O} \\
\text{O} & \quad \text{Na} \\
\text{OH} & \quad \text{Ac} \\
R'' & 
\end{align*}
\]

Haynes and Stanners (J., 1956, 732, 4103) have found diisopropylaminomagnesium bromide to be a more efficient reagent than sodium for effecting a similar internal Claisen condensation in esters of hydroxy esters particularly where hydroxyl group is tertiary. They obtained good yields of tetronic acids in which \( R', R'' \) and \( R''' \) were \( H, \) alkyl or aryl groups.

\[
\begin{align*}
\text{EtOOC} & \quad \text{CH}_2\text{R''} \\
R'R'' & \quad \text{O} \\
\text{O} & \quad \text{R''} \\
\text{OH} & \quad \text{R''} \\
\end{align*}
\]

These were the methods which were available for preparing tetronic acid derivatives. Since one intention of this work was to investigate further the aromatic substitution reactions of the tetronic acid nucleus, a supply of tetronic acid
derivatives with free $\alpha$-positions was necessary. The methods applicable were therefore those of Anschütz et al. and Benary (loc. cit.) and of Haynes and Stammers (loc. cit.).

$\alpha$-Methyltetronic acid was also required for the preparation of ethers.

$\gamma$-Phenyltetronic acid was prepared by the method of Haynes et al., which is a modification of Benary's method. Acetylmandelyl chloride in ethereal solution was added dropwise to the magnesio-derivative prepared by reaction of magnesium methoxide 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. Careful decomposition with ice and sulphuric acid followed by extraction gave a yellow oil which on standing eliminated ethyl acetate to give $\alpha$-carbethoxy-$\gamma$-phenyltetronic acid. This was boiled with 10% alkali, and acidification gave evolution of carbon dioxide and precipitation of $\gamma$-phenyltetronic acid. The product was crystallised from water and had m.p. 126°. In this way $\gamma$-phenyltetronic acid was obtained in yields of 65 - 70%.

Just as successful was an adaptation of this method to give $\gamma$-methyltetronic acid, although Benary's method itself, involving cyclisation of the product of condensation of bromopropionyl bromide and sodium diethyl malonate, is found to give poor yields (Clutterbuck, Raistrick and Reuter, Biochem. J., 1935, 29, 1300). Acetylglactyl chloride was treated in the same way as the acetylmandelyl chloride in the last preparation, except that
rather milder conditions of alkaline hydrolysis were employed and that the greater solubility in water of the γ-methyltetronic acid necessitated continuous extraction of aqueous layers with ethyl acetate. In this way γ-methyltetronic acid was prepared in 70% yield. The product was not quite chromatographically pure until crystallised from benzene/light petroleum, when it had m.p. 112 - 113° and gave reactions typical of tetronic acids.

Clutterbuck et al. (loc. cit.) prepared γ-methyltetronic acid in 27% overall yield by heating in vacuo the α-γ-dibromo derivative of ethylpropionylacetate and catalytically reducing the α-bromo-γ-methyltetronic acid so formed.

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{COCH}_2\text{COOEt} & \quad \longrightarrow \quad \text{CH}_3\text{CHBr.CO.CHBr.CO} \text{OEt} \\
\end{align*}
\]

Three other α-unsubstituted tetronic acids were prepared, using the method of Haynes and Stanners (loc. cit.) in cyclising esters I - III.

\[
\begin{align*}
\text{I} & \quad \text{II} & \quad \text{III} \\
\end{align*}
\]

α,α-Diphenyltetronic acid was prepared by the cautious addition of an ethereal solution of methyl acetoxydiphenylacetate (I), prepared by acetylation of methyl benzilate, to an ethereal
suspension of diisopropylammonium bromide. The mixture was allowed to stand overnight and was then hydrolysed with ice-cold sulphuric acid. Thorough extraction with ether, washing of the extracts with aqueous sodium hydrogen carbonate solution, and acidification of the washings precipitated ££-diphenyltetronic acid in 78% yield. The product was crystallised from ethanol when it had m.p. 212° and had the properties typical of the tetronic acids.

££-Dimethyltetronic acid was prepared in a similar fashion in 65% yield from ethyl α-acetoxy-α-methylpropionate (II). It was found that this ester was obtainable in higher yields by acetylation of ethyl α-hydroxy-α-methylpropionate, prepared from the cyanhydrin, than by treatment of ethyl 2-bromoisobutyrate with potassium acetate. After crystallisation from benzene the ££-dimethyltetronic acid had m.p. 140 - 141°.

£-Spirocyclohexyltetronic acid was also prepared by the same method, but here the preparation of the ester (III) was consistently less successful. Although obtained in quite good yields with the boiling-point and refractive index given in the literature for ethyl 1-acetoxy-cyclohexane-1-carboxylate, the ester had properties indicative of unsaturation and cyclised to give the tetronic acid in a yield of only 23%. This was recrystallised from aqueous ethanol and had m.p. 195°. It seems probable that during the conversion of the cyclohexanonecyanhydrin to the ethoxycarbonyl compound a cyclohexene derivative was formed.

α-Methyltetronic acid was prepared by brominating ethyl
\( \alpha \)-methylacetooacetate in chloroform solution and heating the product \textit{in vacuo} on a steam-bath, when slightly impure crystalline \( \alpha \)-methyltetronic acid was obtained in 73\% yield. This was recrystallised from water, when it had m.p. 188 - 189\( ^\circ \).
Yields are reported as the percentage of the theoretical yield. All melting points were recorded on a Kofler block and are uncorrected. Analyses are due to Drs. Weiler and Strauss, Oxford.

Ultraviolet spectra were determined using the Unicam S.P. 500 spectrophotometer. Absolute ethanol was purified by refluxing with sodium and redistilling.
(i) *Ethyl $\alpha$-methylacetooacetate (I)*

Freshly cut sodium (92 g., 4 g. atoms) was placed with absolute ethanol (300 ml.) in a 3 l. flask fitted with a mercury-sealed stirrer, dropping-funnel and reflux condenser (guard-tubes). When the reaction had moderated, more ethanol (1200 ml.) was added in portions to complete the solution of the sodium. Freshly distilled ethyl acetooacetate (520 g., 4 mol.) was then introduced and immediately afterwards methyl iodide (580 g., 4.1 mol.) was added dropwise during 1 hour and the mixture was placed on a steam-bath overnight. The bulk of the ethanol was distilled off with stirring to prevent bumping and enough water was added to the cooled mixture to dissolve the sodium iodide precipitate. A thorough extraction with ether was carried out, the extract was dried ($\text{Na}_2\text{SO}_4$), the solvent removed, and the residual liquid distilled under reduced pressure. A fore-run was collected (48 g.), followed by ethyl $\alpha$-methylacetooacetate (477 g., 83%), b.p. 81 - 82°/16 mm., n$^D_{17}$ 1.4211 (Brühl, J. pr. Chem., 1894, (2), 50, 128, gives b.p. 80 - 80.5°/14 mm.).

(ii) *Ethyl $\gamma$-bromo-$\alpha$-methylacetooacetate (II).*

Ethyl $\alpha$-methylacetooacetate (477 g., 3.31 mol.) was dissolved in chloroform (1000 ml.) and a solution of bromine (529 g., 3.31 mol.) in chloroform added during 2 hours (cf. Hof, Ann.,...
For the next hour the mixture was refluxed (much HBr was evolved) and then most of the chloroform was distilled off at atmospheric pressure.

(iii) \( \alpha \)-Methyltetronic acid (III).

The partly solid mixture was allowed to stand for 2 hours, and then heated in vacuo on the steam-bath for 12 hours. It was then cooled and filtered. The solid was washed with chloroform and ether, giving \( \alpha \)-methyltetronic acid (272 g., 73%) as an off-white crystalline solid. The filtrate deposited more acid on standing and cooling. Recrystallisation from water (500 ml.) gave \( \alpha \)-methyltetronic acid as needles, m.p. 188 - 189°. (Demarquay, Bull. Soc. chim., 1880, (2), 33, 521, gives m.p. 189°.)

\( \alpha \)-Phenyltetronic Acid. (Haynes, Flimner and Stanners, J., 1956, 893, 4661.)

\[
\begin{align*}
\text{Ph.CH(OOCH}_3\text{)COCl} & \quad \text{I} \\
+ \text{COOEt} \quad \rightarrow \quad \text{Ph.CH(OOCH}_3\text{)CO.CH(COOEt)}_2 & \quad \text{II}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} \quad \text{III} & \quad \rightarrow \quad \text{Ph} \quad \text{IV}
\end{align*}
\]
(1) Acetylmandelyl chloride (I). (Org. Syntheses, I, 12)

A mixture of mandelic acid (100 g., 0.66 mol.), acetic anhydride (100 g., 0.96 mol.) and 2 drops conc. \( \text{H}_2\text{SO}_4 \) was allowed to stand for one hour. Water (400 ml.) was added, and the mixture was allowed to stand overnight. The acid monohydrate separated as an oil which was crystallised by scratching the side of the vessel. The solid was collected, dried in vacuo, dissolved in toluene (500 ml.) and the aqueous layer which formed was separated. The toluene solution was dried (\( \text{Na}_2\text{SO}_4 \)) and distilled until a syrup remained which began to crystallise.

This syrup was treated with thionyl chloride (160 g.) and refluxed for 1 hour. After standing overnight the mixture was distilled, and the fraction b.p. 99 - 103\(^\circ\)/0.05 mm. was collected. (Lit. b.p. 125 - 130\(^\circ\)/10 mm.). Yield 112 g. (83%).

(ii) Diethyl acetylmandelylmalonate (II).

In a 3-necked 2 l. flask fitted with a reflux condenser (guard-tube), a stirrer and a separatory funnel was placed ether-washed magnesium (12 g., 0.5 mol.), activated by heating with a little mercuric chloride. This was refluxed for 2.5 hours with dry methanol (40 ml.), more methanol (10 ml.) was added, and diethyl malonate (80 g., 0.5 mol.) in dry ether (40 ml.) was added gradually, a vigorous reaction occurring. The mixture was allowed to reflux spontaneously for 0.5 hour and then was heated on a water-bath to distil off the ether and to dissolve residual magnesium. Dry toluene (100 ml.)
was added and the mixture was refluxed for 4 hours. Finally all alcohol was removed by adding dry toluene (300 ml.) and distilling in vacuum, and repeating the procedure with a further 200 ml. toluene.

The resultant grey syrup was treated with dry ether (300 ml.) and freshly distilled acetylmandelyl chloride (106 g., 0.5 mol.) dissolved in dry ether (120 ml.) was added, with stirring and shaking, at such a rate as to promote gentle reflux. A greenish-white syrup finally separated. The mixture was refluxed for 0.5 hour and hydrolysed by cautious addition of portions of chopped ice (300 g.) and sulphuric acid (100 ml. of 30% by vol.). Thorough extraction with ether and drying and distillation of the extracts left a yellow oil (160 g.) which gave a red colour with ferric chloride.

When this oil was allowed to stand for a few days it cyclised and crystallised to give 2-ethoxycarbonyl-γ-phenyltetronic acid (III), which after recrystallisation from ethyl acetate had m.p. 145°. (Anschütz and Böcker, Ann., 1909, 368, 53, give m.p. 140°). In ethanol this substance had $\lambda_{\text{max}}$ 2500 $\AA$, log $\varepsilon_{\text{max}}$ 4.25.

(iii) $\gamma$-Phenyltetronic acid (IV).

The oil was allowed to stand for 1 hour with sodium hydroxide solution (700 ml. of 10%) and the solution was then refluxed for 3 hours. After cooling, the solution was slowly made acid by addition of sulphuric acid (50%) which precipitated, with effervescence, white crystals and oil of $\gamma$-phenyltetronic
acid. After 10 minutes it was collected by filtration, the filtrate yielding a further appreciable amount by cooling and ether extraction. The crude product (65 g.) was recrystallised from boiling water (3 l.) and was obtained as cream-white crystals, m.p. 126°. Yield 57 g. (69%). Yields from different preparations ranged from 65% to 70%. With aqueous sodium nitrite the acid gave a purple colour. In ethanol it had $\lambda_{\max} = 2520 \AA$, $\log \varepsilon_{\max} = 4.25$.

**\( \alpha \times \alpha \)-Diphenyltetronic Acid.** (Haynes and Stanners, J., 1956, 792, 4105).

\( \begin{array}{ccc}
\text{Ph} & \text{COOMe} & \text{Ph} \\
\text{Ph} & \text{OH} & \text{Ph} \\
\text{Ph} & \text{COOMe} & \text{Ph} & \text{COCH}_3 \\
\text{I} & \rightarrow & \text{II} & \rightarrow & \text{III}
\end{array} \)

(i) **Methyl benzilate.** (Acres, Ber., 1904, 37. 2765).

Benzil (330 g., 1.57 mol.) was refluxed with potassium hydroxide (330 g.) in water (700 ml.). Hydrolysis of the potassium salt gave benzilic acid (253 g., 70%).

Benzilic acid (250 g., 1.1 mol.) was refluxed for 8 hours in absolute methanol (1900 ml.) containing conc. sulphuric acid (90 ml.) and then the bulk of the excess of methanol distilled off. The remaining acid was neutralised with sodium carbonate and 3 volumes of water added, causing separation of the ester as a yellow oil which solidified on standing. The crude ester was purified by solution in ethanol and precipitation with water. Recrystallisation from light
petroleum (b.p. 60 - 80°) gave the pure ester (I)
(175 g., 68%), m.p. 73 - 74° (lit. m.p. 73°).

(ii) Methyl \( \alpha \alpha \)-diphenyl-\( \alpha \)-acetoxyacetate (II) (King and Holmes, J., 1947, 164).

Methyl benzilate (121 g., 0.5 mol.) was mixed with
freshly distilled acetic anhydride (250 g., 2.5 mol.)
containing conc. sulphuric acid (5 ml.). The mixture was
heated on a steam-bath for 36 hours. After thorough cooling
a brown crystalline solid was collected by filtration and
washed with water. Recrystallisation thrice (charcoal) from
ethanol gave the ester (II) (102 g., 72%), m.p. 122°,
(Herzig and Schleiffer, Ann., 1920, 422, 331, give
m.p. 122 - 125°).

(iii) \( \alpha \alpha \)-Diphenyltetronic acid (III)

Methyl \( \alpha \alpha \)-diphenyl-\( \alpha \)-acetoxyacetate (57 g., 0.2 mol.)
suspended in an ether/toluene mixture (200 ml. of 50 : 50,
V : V) was added during 40 minutes to an ethereal suspension
of diisopropylaminomagnesium bromide prepared according to
the method of Frostick and Hauser (J. Amer. Chem. Soc.,
1949, 71, 1350) from magnesium (9.7 g., 0.4 g. atom), ethyl
bromide (43.6 g., 0.4 mol.), and diisopropylamine
(40.4 g., 0.4 mol.). The white mixture was allowed to stand
overnight and was hydrolysed at 0° with sulphuric acid
(500 ml. of 15%) and extracted thoroughly with ether and
chloroform. The combined extracts were washed with aqueous
sodium hydrogen carbonate; acidification of the washings
precipitated \( \gamma \)-diphenyltetronic acid (34 g., 78%) m.p. 212\(^\circ\) from ethanol (100 ml.). (Leccog. Compt. rend., 1946, 222, 239, gives m.p. 212\(^\circ\); Lacey, J., 1954, 839, gives m.p. 213\(^\circ\)). With aqueous sodium nitrite and dilute hydrochloric acid it gave a blue colour. In ethanol it had \( \lambda_{\text{max}} \) 2580 \( \AA \), \( \varepsilon_{\text{max}} \) 15,810.

\( \gamma \)-Methyltetronic Acid.

\[
\text{CH}_3\text{CH(OOCCH}_3\text{)COCl}
\]

\[
\begin{array}{c}
\text{I} \\
\text{+ COOMe} \\
\text{III}
\end{array}
\]

(1) Acetyllactyl chloride (I)

The acetylation method of Filachione and Fisher (U.S.P., 2, 399, 395; Chem. Abs., 1946, 4394) was followed. Lactic acid (200 g., 2.2 mol.) was mixed with glacial acetic acid (2000 g.), acetic anhydride (224 g., 2.2 mol.), and hydrochloric acid (8.5 g.) and heated on a boiling water-bath for 8 hours. The mixture was set aside for 4 days and distilled, and the fraction with b.p. 145 - 160\(^\circ\)/15 mm. collected (70 g., 25%). (Lit. b.p. 127\(^\circ\)/11 mm.).

The acetyllactic acid was refluxed with thionyl chloride (180 g.) for 2.5 hours, and the resulting mixture distilled. The fraction boiling at 76 - 86\(^\circ\)/15 mm. was the chloride (I) and was collected (55 g., 68%). (Lit. b.p. 56\(^\circ\)/11 mm).
(ii) \( \gamma \)-Methyltetronic acid (II).

Acetyllactyl chloride (50 g., 0.33 mol.) in dry ether was added with stirring during 1 hour to a solution in dry ether (100 ml.) of diethyl methoxymagnesiomalonate, from magnesium (8 g., 0.33 mol.), dry methanol (30 ml.) and diethyl malonate (54 g., 0.33 mol.). A viscous yellow complex separated. The mixture was refluxed on a water-bath for 0.5 hour and allowed to stand overnight. Hydrolysis at 0° with sulphuric acid (100 ml. of 30% by vol.) was followed by continuous extraction with ethyl acetate for 12 hours. Distillation of the extract in vacuo left an oil which was allowed to stand for 4 hours with aqueous sodium hydroxide (400 ml. of 10%) and then heated under reflux in a boiling water-bath for 2 hours. Cooling and acidification with sulphuric acid (50% by vol.) gave some effervescence and a lightening in colour. Extraction with chloroform, followed by continuous extraction with ethyl acetate for 12 hours and drying and distillation of the combined extracts left a semi-crystalline oil. This crystallised from benzene/light petroleum (b.p. 60 - 80°) as cream-coloured plates (II), m.p. 112 - 113° after 3 recrystallisations. (Clutterbuck, Raistrick and Reuter, Biochem. J., 1935, 29, 1300, give m.p. 115 - 117°.) Yield 27 g., (71%). It gave a deep purple nitrite test.
**Yb-Dimethyltetronic Acid.** (Haynes and Stanners, loc. cit.).

\[
\begin{align*}
\text{Me} & \quad \text{CN} \quad \rightarrow \quad \text{Me} & \quad \text{COOEt} \\
\text{Me} & \quad \text{OH} \quad \rightarrow \quad \text{Me} & \quad \text{OH} \\
\text{Me} & \quad \text{O} \quad \rightarrow \quad \text{Me} & \quad \text{O, CO, CH}_2 \\
\end{align*}
\]

(I) **Ethyl α-hydroxy-α-methylpropionate (II).**

Sulphuric acid (550 ml., 30% by wt.) was slowly introduced into a stirred solution of sodium cyanide (94 g., 2 mol.) in acetone (116 g., 2 mol.) and water (400 ml.) with cooling so that the temperature remained below 15 - 20°C. When the addition was complete, the mixture was stirred for a further 15 minutes, and then thoroughly extracted with ether. The extract was dried \((\text{Na}_2\text{SO}_4)\), the solvent removed under reduced pressure, and the residue of crude acetonecyanhydrin (I) dissolved in an equal volume of absolute ethanol. The solution was saturated with dry hydrogen chloride and refluxed until no more ammonium chloride separated. The precipitate was removed by filtration, and the processes of saturation and refluxing repeated twice, until no more ammonium chloride separated, showing that ethanolysis of the cyanide group was complete. After removal of the ammonium chloride, the solution was neutralised and saturated with aqueous sodium hydrogen carbonate and thoroughly extracted with ether. The extract was dried \((\text{Na}_2\text{SO}_4)\) and the solvent removed under reduced pressure. Distillation of the residual liquid through a 6" Dufton column gave the ester (II)

(ii) Ethyl \( \alpha \)-acetoxy-\( \alpha \)-methylpropionate (III).

Ethyl \( \alpha \)-hydroxy-\( \alpha \)-methylpropionate (106 g., 0.8 mol.) was allowed to stand for 24 hours with acetic anhydride (123 g., 1.2 mol.) and 2 drops of concentrated sulphuric acid. The mixture was heated at 80° for 1.5 hour and then cooled and diluted with chloroform. The solution was washed with aqueous sodium hydrogen carbonate, dried (Na\textsubscript{2}SO\textsubscript{4}) and distilled to give the ester (III) (84 g., 60%) b.p. 76 - 77°/10 mm., n\textsubscript{D}^{20} \, 1.4089.

Alternative preparation.

A mixture of ethyl 2-bromo isobutyrate (10 g., 0.05 mol.) and anhydrous potassium acetate (20 g., 0.2 mol.) in absolute ethanol (200 ml.) was refluxed in a water-bath for 12 hours, cooled, diluted with water and the solution extracted with ether. The extract was dried (Na\textsubscript{2}SO\textsubscript{4}) and distilled, the fraction with b.p. 70 - 71°/9 mm. being collected (1.6 g., 18.4%), n\textsubscript{D}^{19} \, 1.4102.

(iii) \( \alpha \alpha \)-Dimethyldieutronic acid (IV).

Ethyl \( \alpha \)-methyl-\( \alpha \)-acetoxypropionate (85 g., 0.5 mol.) in dry ether (200 ml.) was added during 1.5 hour to an ethereal suspension of diisopropylaminomagnesium bromide from magnesium (17 g., 0.7 g. atom), ethyl bromide (77 g., 0.7 mol.), and diisopropylamine (71 g., 0.7 mol.). The mixture was refluxed
for a further 30 minutes and allowed to stand overnight, and then hydrolysed and extracted as before. Continuous extraction for 24 hours with ethyl acetate of the acidified sodium hydrogen carbonate extract gave \( \text{\(\text{\(\text{\(\text{\(\text{x}\)-dimethyltetronic acid (42 g., 65\%)}\)}}\)}}\) (Benary, Ber., 1907, 40, 1082, gives m.p. 142 - 143°; Jones and Whiting, J., 1949, 1422, gives m.p. 142°). It gave a purple colour with aqueous sodium nitrite; no immediate colour with aqueous ferric chloride.


Concentrated hydrochloric acid (150 ml.) was added during 1.5 hour to a stirred mixture of cyclohexanone (100 g., 0.93 mol.) and potassium cyanide (97 g., 1.5 mol.) in ether (250 ml.), kept below 0°. The reaction mixture was stirred for a further 6 hours and then sufficient water added to dissolve the solid matter present, the ether layer separated, and the aqueous layer extracted with ether. The ether layers were combined and washed with saturated aqueous sodium hydrogen sulphite.
containing an excess of $\text{SO}_2\text{O}_4^-$, then with sodium hydrogen carbonate and water and the extract dried ($\text{Na}_2\text{SO}_4$).

Filtration and evaporation of the solvent gave crude cyclohexanonecyanhydrin, which was dissolved in an equal volume of absolute ethanol and the solution saturated with dry hydrogen chloride. The mixture was refluxed until esterification was complete. The ammonium chloride was removed by filtration, and the processes of saturation and refluxing repeated (twice) until no more ammonium chloride was precipitated. The solution was filtered, neutralised with sodium hydrogen carbonate, saturated with sodium chloride and the ester extracted into ether. The extract was dried ($\text{Na}_2\text{SO}_4$), and distilled under reduced pressure, giving the ester (I) (87 g., 50%) b.p. 95 - 100°/15 mm., $n_D^{17}$ 1.4556 (v. Auwers and Krollpfefifer, Ber., 1915, 48, 1392; give b.p. 99 - 101°/15 mm., $n_D^{17}$ 1.4568).

(ii) **Ethyl 1-acetoxy-cyclohexane-1-carboxylate (II).**

A mixture of ethyl 1-hydroxy-cyclohexane-1-carboxylate (86 g., 0.5 mol.), acetic anhydride (75 g., 0.75 mol.) and concentrated sulphuric acid (0.5 ml.) was set aside for 5 hours and then refluxed for 15 minutes to complete the reaction. Ether was added and the solution washed with aqueous sodium hydrogen carbonate until no more carbon dioxide was evolved. The ether solution was washed with water and dried ($\text{Na}_2\text{SO}_4$). Removal of the solvent and distillation of the residue gave the ester (II) (81 g., 74%).
b.p. 117 - 121°/10 mm., n^D_20 1.4499 (Lit.: b.p. 122°/10 mm., 

n^D_10 1.4484).

(iii) \(\gamma\)-Spiro cyclo hexyltetronic acid (III).

Ethyl 1-acetoxycyclohexane-1-carboxylate (505 g., 0.375 mol.) 
in dry ether (125 ml.) was added during 1 hour to an ethereal 
suspension of diisopropylamino magnesium bromide from magnesium 
(12.2 g., 0.5 g. atom), ethyl bromide (55 g., 0.5 mol.) and 
diisopropylamine (50.5 g., 0.5 mol.); a light green sticky 
mass separated. The mixture was refluxed for a further 1.5 hour 
and left to stand overnight. Hydrolysis and extraction finally 
of the acidified sodium hydrogen carbonate extract with ethyl 
acetate gave \(\gamma\)-spirocyclohexyltetronic acid (14 g., 23%); 
prisms from aqueous ethanol, m.p. 195 - 196° (Jones and Whiting, 
loc. cit., give m.p. 198°; Stanners, loc. cit., gives m.p. 
195 - 196°). With aqueous sodium nitrite it gave a light purple 
colour. The original ethereal extract, containing only neutral 
and basic substances, was dried (Na_2SO_4) and distilled at 
reduced pressure, yielding a fraction with b.p. 114 - 117°/10 mm. 
(53 g.). This material, after being redistilled, was used in a 
further attempt at cyclisation but was recovered unchanged and 
almost undiminished. It was found to decolourise bromine water 
at once.

Pyronone. (Collie, J., 1891, 52, 607).

Dehydracetic acid (50 g., 0.3 mol.) in sulphuric acid 
(150 g. of 90% v : v) was heated slowly to 130°, maintained at 
that temperature for 7 minutes and then cooled. The mixture
was poured into ice-cold water (200 ml.), crystallisation occurring after 2 minutes. The solid (25 g., 67%) was collected and recrystallised from dioxan, m.p. 184 - 185°. (Collie gives m.p. 188°). With aqueous sodium nitrite it gave a deep blue colour, and with ferric chloride an orange colour. In ethanol it had $\lambda_{\text{max}}$, 2600 Å, $\log \varepsilon_{\text{max}}$, 3.89.
SECTION II.

THE ETHERS OF TETRONIC ACIDS.
II. Ethers of Tetrone Acids.

Introduction.

In an attempt to settle the controversy on the keto-enol constitution of acetoacetic ester Freer (Amer. Chem. J., 1891, 13, 313; ibid., 1895, 17, 795) undertook a study of the methylation of $\alpha$-methyltetronic acid, the structure of which was similar to that of acetoacetic ester. He found that although $\alpha$-methyltetronic acid gave a stable sodium salt this would not react with alkyl halides under the conditions which give C-alkylation of acetoacetic ester. This has since been confirmed by Kumber (J. Amer. Chem. Soc., 1938, 60, 2532).

Freer also found that $\alpha$-methyltetronic acid underwent O-acetylation and in contrast to ethyl acetoacetate was not reduced by sodium amalgam. He interpreted these results as showing that the acid contained an enolic hydroxyl group in place of the keto-group present in the ester.

In the accounts which have since appeared describing the preparation of ethers of $\alpha$-methyltetronic acid, by means of the silver salt and alkyl halides or by diazomethane, there are considerable discrepancies. The accounts are tabulated.
<table>
<thead>
<tr>
<th>Ref.</th>
<th>Reagents</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Ag α-methyltetronate + MeI in benzene.</td>
<td>Liquid b. 215 – 220°.</td>
</tr>
<tr>
<td>2.</td>
<td>α-Methyltetronic acid + diazomethane.</td>
<td>Liquid b. 160 – 170°/15 mm.</td>
</tr>
<tr>
<td>3.</td>
<td>– do. –</td>
<td>Solid m.p. 84 – 85°.</td>
</tr>
<tr>
<td>4.</td>
<td>α-Methyltetronic acid + EtOH/HCl.</td>
<td>Solid m.p. 30°; b.p. 180°/70 mm.</td>
</tr>
<tr>
<td>5.</td>
<td>Ag α-methyltetronate + EtI (sealed tube).</td>
<td>a) Liquid b. 175 – 176°/50 mm.</td>
</tr>
<tr>
<td>6.</td>
<td>– do. –</td>
<td>b) Solid m.p. 29°; b.p. 180°/43 mm.</td>
</tr>
</tbody>
</table>


The solid ethyl ether Cornelius and Moscheles found to be comparatively stable to alkali, while Freer found that the liquid ethyl ether was hydrolysed to α-methyltetronic acid by standing overnight with alkali. The solid methyl ether Stodola et al. found to be quite unstable as it was hydrolysed by water in 5 minutes at 100° or overnight at room temperature.
Stodola et al. assumed that this solid methyl ether was a normal tetronic acid enol ether typical in its U.V. light absorption and stability, and since a methylated derivative of a naturally occurring lactonic acid which they isolated was quite different they discounted the possibility that the naturally occurring acid could have a tetronic acid structure. This acid, which they named zymonic acid, is produced when the yeasts *Trichosporon capitatum*, *Hansenula subpelliculosa* and *Kloeckera brevis* are grown on a medium containing glucose.

Free zymonic acid is unstable and was isolated by Stodola et al. by methylation with diazomethane of an ether extract of the mother-liquors. Since the liquid methyl derivative \( \text{C}_8\text{H}_{10}\text{O}_5 \) had stability and U.V. absorption different from those of the "typical" tetronic acid ether they assigned to the isolated derivative the structure (I) and to the free acid the equilibrium structures (II) and (III).

\[
\text{I} \quad \text{II} \quad \text{III}
\]

However, some light has been thrown on the situation by A. H. Stanners (Ph.D. Thesis, Edin, 1956) who has pointed out that the absorption characteristics and stability of the dimethylzymonic acid are indeed typical of the properties of
tetronic acid ethers and that the solid methyl ether of 
α-methyltetronic acid is the abnormal ether. He repeated
the methylations by the silver salt method of Conrad and
Gast and by the diazomethane method of Stodola et al.,
and isolated in all three methyl ethers of α-methyltetronic
acid. The silver salt method gave in a ratio of about
1 : 2 the normal enol ether (IV) and what he suggested
was αα′-dimethyl-β-oxobutyrolactone (V). This was the
first time that α-alkylation had been reported in
tetronic acid chemistry.

Using diazomethane, Stanners obtained along with
the enol ether (IV) the solid product described by Stodola
et al., although the analysis was not quite satisfactory.
The structure (VI) was assigned to this ether.

![IV](image1)

![V](image2)

![VI](image3)

We must therefore conclude that the tetronic acid
anion has significant contributions from the canonical
forms (VII - IX) and that a methylation product
corresponding to each canonical form can be prepared.
In the work now to be described, the conclusions reached by Stannier were confirmed and extended. The ethers of some substituted tetronic acids were prepared by different methods and the stability of some of the methyl ethers investigated. A discussion of infra-red absorption spectra is appended.

**Methylation by Dimethyl Sulphate.**

The methyl ethers of \( \alpha \)-methyltetronic acid, \( \chi \)-spirocyclohexyltetronic acid, \( \psi \psi \)-dimethyltetronic acid, \( \chi \)-phenyltetronic acid and \( \psi \psi \)-diphenyltetronic acid were prepared by dissolving the acid in a slight excess of 15% aqueous sodium hydroxide solution and adding dropwise a 50% excess of dimethyl sulphate. The mixture was stirred for several hours at room temperature and extracted with ether. The ether extract was washed with aqueous sodium hydrogen carbonate, dried, and distilled at reduced pressure to give the ethers. Only one product was obtained in each case, the yields varying between 33 and 75%. The analytically pure diphenyltetronic acid ether showed no maximum above 2200 \( \lambda \) in its U.V. light absorption (log \( \varepsilon \) 4.2 at 2200 \( \lambda \)).

**Methylation by Diazomethane.**

Diazomethane was prepared by the method of de Boer and Backer (Rec. Trav. chim., 1954, 73, 229) from \( p \)-tolylsulphonylmethylacetamide. Three tetronic acids
were methylated by suspending them in dry ether and adding an ethereal solution of diazomethane. The reaction mixture was filtered and distilled at reduced pressure. In this way \( \gamma \)-phenyltetronic acid methyl ether was obtained as a residue and recrystallised from ethyl acetate/light petroleum. The ether was completely stable and even after standing for some weeks contained no free tetronic acid. The same treatment of \( \gamma \gamma \)-diphenyltetronic acid gave the pure methyl ether as a residue which was recrystallised from methanol, and was identified using m.p. and U.V. light absorption with the product from dimethyl sulphate methylation.

\( \alpha \)-Methyltetronic acid was similarly methylated (cf. Stodola et al., loc. cit.). The residue after removal of solvent was distilled at reduced pressure, when a colourless solid accumulated in the condenser while a colourless distillate was microfractionated to give three fractions almost identical in b.p. (82 - 84°/0.03 mm.) and refractive index (Calam, Todd and Waring, loc. cit., give 160 - 170°/15 mm.). The first and third fractions gave identical I.R. absorption spectra. The solid product which sublimed readily was recrystallised four times from dry ether as long needles m.p. 79 - 81° (Stodola et al. give m.p. 84 - 85°). On standing for some days the substance gave impure \( \alpha \) -methyltetronic acid, m.p. 183 - 184°. A sample of the freshly-prepared solid product gave a purple colour with sodium nitrite solution and I.R. absorption spectra distinct
from those of the normal enol ether and of authentic
$\beta$-dimethyl-$\beta$-oxobutyrolactone. With some difficulty it
gave an oxime which decomposed at about $150^\circ$. Analysis
results were unsatisfactory. (Found: C, 54.91; H, 6.18.
Calc. for $C_6H_8O_3$: C, 56.26; H, 6.29%).

Ethylation by Diazoethane.

Kende (Chem. and Ind., 1956, 1053) has reformulated two
isomeric compounds formed in the reaction of diphenylketen
and ethyl diazoacetate (Staudinger and Beber, Helv. Chim. Acta,
1921, 4, 3) as (X) and (XI). In support of structure (XI) he
cites infra-red absorption and ease of hydrolysis characteristic
of keten-acetals. The compounds hydrolysed readily to
\[ \text{XIII} \]

$\text{X}$

$\text{XI}$

$\text{XII}$

Structure (XI) is comparable to the keten-acetal type of
structure proposed by Stamers (loc. cit.) for the solid methyl
ether of $\alpha$-methyltetronic acid. If the form of $\gamma\delta$-diphenyl-
tetronic acid corresponding to (IX) gives appreciable
contribution to the resonance, then the compound (XI) should be
produced by the action of diazoethane on $\gamma\delta$-diphenyltetronic
acid.
The method of de Boer and Backer (loc. cit.) for preparing diazomethane was adapted to give diazomethane. The solution of diazomethane was added slowly to a suspension of \( \gamma\gamma \)-diphenyltetronic acid in dry ether. Nitrogen was evolved, and the yellow solution was allowed to stand for only an hour, when a pale yellow non-crystalline material was collected by filtration and stored in a desiccator. More of the same solid was obtained by removal of the solvent. Both portions were hygroscopic, gave positive nitrite tests, and were soluble in aqueous sodium bicarbonate solution, acidification giving \( \gamma\gamma \)-diphenyltetronic acid. The compound contained no nitrogen. No dependable m.p. (>100°F) or i.r. spectra could be obtained, but U.V. absorption spectra were obtained and showed one maximum at 2570 \( \AA \), \( \lambda \) \( \text{max} \) 12,620. Kende (loc. cit.) for compound (XI) gives m.p. 125 - 126°F and \( \lambda \) \( \text{max} \) 2560 \( \AA \), \( \epsilon \) \( \text{max} \) 13,800. ( \( \gamma\gamma \)-Diphenyltetronic acid has \( \lambda \) \( \text{max} \) 2580 \( \AA \), \( \epsilon \) \( \text{max} \) 15,810). Stodola et al. (loc. cit.) for the solid methyl ether of \( \lambda \)-methyltetronic acid give \( \lambda \) \( \text{max} \) 2670, \( \epsilon \) \( \text{max} \) 18,380.

The product was less stable than that reported by Kende, so that no conclusion can be drawn from these results.
Ethynylation by Ethyl Bromide.

A solution of \(^{10}\)-diphenyltetronic acid in caustic soda did not react with ethyl bromide at room temperature, but refluxing for 5 hours and extracting with ether gave a 9% yield of the crystalline authentic enol ether, m.p. 108 - 110°. This was crystallised to analytical purity from ethanol, when it showed no absorption maximum above 2200 \( \lambda \) (log \( \varepsilon \) max, 4.1).

Silver Salt Alkylation.

When the metallic salt of a compound reacts with an alkyl halide a number of factors influence the position of alkylation. The nature of the solvents and reagents are of course important and Kornblum and his co-workers (Kornblum, Smiley, Blackwood and Iffland, J. Amer. Chem. Soc., 1955, 77, 6269) have recently accounted for the variation in products with the nature of the metallic ion present, and have discussed the mechanism of attack.

According to their theory, if the carbonium content of the transition state is high then the reaction has largely SN1 character and formation of a covalent bond is favoured at the most electronegative point of the anion (O > N > C > S). The smaller the carbonium content of the transition state the greater the SN2 contribution to the reaction and the greater is the preference for C-alkylation, i.e., reaction at the less negative position of the anion. The use of the silver salt of the anion in place of the sodium salt greatly increases the polarisation of the carbon-halogen bond, enhancing the carbonium content of the transition state.
Stanners (loc. cit.) has applied the theory to the reaction of silver \( \alpha \)-methyldtroborate and methyl iodide, and states that the C-alkylation takes place by a second-order attack at the less negative carbon atom, the carbonium content of the transition state being insufficient for SN1 attack on the oxygen atom to predominate.

Kornblum found that, in the alkylation of the silver salt of \( \alpha \)-pyridone, ethyl iodide tended to attack at the position of greatest electron density, i.e. the oxygen atom, whereas methyl iodide gave mainly the N-methyl derivative. It seems that the effect of using the silver salt may have to be reinforced by the influence of hyperconjugation to allow first order kinetics to predominate with attack at the oxygen atom. In the present work silver \( \alpha \)-methyldtroborate was treated with a series of alkyl halides with increasing hyperconjugation. The products were expected to show an increasing proportion of enol ether to C-alkylated compound, although it was realised that such heterogeneous reactions may give un reproduceable results.

It still remained, however, to confirm the identity of the alleged product of C-methylation by comparison with authentic \( \alpha \)-dimethyl-\( \beta \)-oxobutyrolactone (XIV). This was prepared by the method of Reid, Fortenbaugh and Patterson (J. Org. Chem., 1950, \( \text{15} \), 572). Ethyl \( \alpha \)-dimethylacetoacetate was brominated to give ethyl-\( \gamma \)-bromo-\( \alpha \)-dimethylacetoacetate which was treated with anhydrous potassium acetate to give crude ethyl \( \gamma \)-acetoxy-\( \alpha \)-dimethylacetoacetate (XIII) in 78\% yield. This
was allowed to stand with conc. sulphuric acid at 0° for 48 hours, and the mixture was poured on to ice and extracted with chloroform. The extract was washed and dried and distilled at reduced pressure to give authentic 

\[ \text{dd-dimethyl-} \beta \text{-oxobutyrolactone} (\text{b.p. } 41 - 42^\circ/0.07 \text{ mm}, \ n_D^{17} 1.4543). \]  

The oxime was prepared and recrystallised from ethanol, m.p. 132 - 134° (Reid et al. give m.p. 132 - 134°), and the I.R. absorption spectrum of the pure lactone was obtained.

\[
\text{CH}_2(\text{OCOCOCH}_3)_2 \cdot \text{CO}_2 \text{Me} \cdot \text{COEt} \quad \rightarrow \quad \text{Me} \\
\text{Me} \\
\text{Me}
\]

**XIII**

Conrad and Gast's method (loc. cit.) of alkylating silver \( \alpha \)-methyltetronate was repeated using methyl, ethyl and \( \beta \)-butyl iodides. The silver salt of \( \alpha \)-methyltetronic acid was prepared by Freer's method (Amer. Chem. J., 1895, 17, 795) by precipitation with silver nitrate from a concentrated ammoniacal solution of the acid.

The silver salt was heated with methyl iodide in boiling benzene for 6 hours. Filtration and distillation of the filtrate gave two products in the ratio of approximately 1:2, the first of which was the \( \alpha \)-methyl ether as it formed no carbonyl derivatives. The second product gave an oxime, m.p. 132 - 133° undepressed by mixture with the oxime of authentic \( \text{dd-dimethyl-} \beta \text{-oxobutyrolactone}. \) The I.R. absorption spectra of the second product and the authentic lactone were also identical, while the spectrum of the first product was identical with the spectrum of the liquid
methyl ether obtained by means of diazomethane.

A similar experiment using ethyl iodide and heating for 15 hours gave a distillate in five fractions of which the last two slowly crystallised and would not form an oxime. The first two fractions gave the oxime corresponding to \( \alpha\)-methyl-\( \alpha\)-ethyl-\( \beta\)-oxobutyrolactone. The crystalline compound (fraction 4, b.p. 83 - 87\(^\circ\)/0.03 mm.) had an I.R. spectrum corresponding to the normal enol ether; the ketonic product (fraction 1, b.p. 54\(^\circ\)/0.05 mm.) had an I.R. spectrum comparable to those of both authentic \( \alpha\)-dimethyl- and \( \alpha\)-diethyl-\( \beta\)-oxobutyrolactones. The ratio of \( O\)-alkylation to \( C\)-alkylation was about 2:1. Freer (loc. cit.) also isolated two products from the reaction of silver \( \alpha\)-methyltetronate and ethyl iodide in a sealed tube; the first had b.p. 175 - 176\(^\circ\)/50 mm., the second had m.p. 28\(^\circ\) and b.p. 180\(^\circ\)/43 mm.

Treatment of silver \( \alpha\)-methyltetronate with \( t\)-butyl iodide in boiling benzene for 18 hours, filtration and removal of solvent gave an oil containing a small amount of crystalline material. This was purified by dissolving in benzene and heating with charcoal. Filtration and evaporation gave a semi-crystalline substance which formed no ketonic derivatives, and gave some crystalline material in ethyl acetate. These crystals had too low m.p. to be collected and the substance was "short-path" distilled at 100\(^\circ\)/1 mm. The semi-crystalline distillate showed \( \lambda_{max.} \) 2190 \( \AA \), \( \log 24.92 \) - the typical spectrum of an enol ether - and again would not give ketonic
derivatives. (A slight inflection was visible at 2980 R, 
log $\varepsilon$ 3.46, so that the distillate was probably impure.)

**Stability to Hydrolysis of Tetronic Acid Ethers.**

When tetronic acids are dissolved in sodium hydroxide solution anions are produced which are resonance stabilised against further attack by alkali. In the ethers, however, this anion resonance is not possible and it is reasonable to expect that the lactone ring will open in alkali.

The methylated products (with diazomethane) of carolic acid, $\alpha$-acetyl tetronic acid and $\gamma$-methyl tetronic acid vary in their stability to alkali (Clutterbuck et al., Biochem. J., 1935, 29, 300). Carolic acid and $\alpha$-acetyl tetronic acid show ready hydrolysis, ascribed to the presence of 2 $\beta$-carbonyl groups, while the product from $\gamma$-methyl tetronic acid was hydrolysed only slowly by cold $\text{NaOH}$ solution.

Stanners (loc. cit.) noted that the normal methyl ether of $\alpha$-methyl tetronic acid is stable to boiling with water for 20 hours, but in sodium hydroxide the uptake tended to a steady limit after a few hours corresponding to one part of $\text{NaOH}$ used up by either hydrolysis of the ether group or ring-opening.

In our work the methyl ethers of some tetronic acids, prepared by means of dimethyl sulphate, were allowed to stand at room temperature with a slight excess of standard sodium hydroxide with enough ethanol for solution. Back-titration at intervals with standard hydrochloric acid allowed the extent
of hydrolysis of the ether to be calculated. The ethers of \( \gamma \)-spirocyclohexyltetronic acid and of \( \gamma\gamma \)-diphenyltetronic acid were found to be unchanged after standing for a day with sodium hydroxide. \( \alpha \)-Methyltetronic acid methyl ether after 1 hour had neutralised 1 equivalent of NaOH, as had the ethers of \( \gamma \)-phenyltetronic acid and \( \gamma\gamma \)-dimethyltetronic acid, and the products of the last two hydrolyses were shown chromatographically to be the intact parent tetronic acids.

It seems that no generalisation can be made regarding the stability of the enol ethers, but where they are hydrolysed by alkali only the ether link is broken and the intact parent tetronic acid is generated. In the enol ethers, then, the lactone ring is still comparatively stable.
DISCUSSION.

Absorption spectra give a good indication of the position of alkylation in a tetronic acid. The undissociated enols of free tetronic acids show one maximum only at 2150 - 2300 Å in water and in 1N HCl (log $\varepsilon$ 4.2) (Plimmer, op. cit., p.143; Stanners, loc. cit.) and a similar maximum is shown by enol ethers (Raphael, J., 1949, 118) in ethanol. In ethanol and 1N NaOH free tetronic acids show only one peak corresponding to the tetronic acid anion, at 2500 - 2600 Å, log $\varepsilon$ 4.3 approx.. Although maxima at or below 2200 Å may be ill-defined, the intensity of absorption by the enol ethers distinguishes them from the $\alpha\alpha$-disubstituted tetronic acids, which show a very low intensity of absorption (log $\varepsilon$ at 2300 Å approx. 2.0) decreasing above 2200 Å with no maximum (Plimmer, op. cit., p.143). Thus spectra in ethanol afford a means of distinguishing acidic tetronic acids from $\alpha\alpha$-dialkyltetronic acids and the enol ethers.

Maxima were found at about 2200 Å with comparatively strong absorption (log $\varepsilon$ 4.0 approx.) for the products obtained using the sodium salts of tetronic acids in ethanol ($\gamma$-phenyltetronic acid with allyl bromide and $\alpha$-propyl bromide) and in water ($\gamma\gamma$-diphenyltetronic acid with ethyl bromide and dimethyl sulphate) so that these were enol ethers. U.V. absorption typical of enol ethers was also given by the single products of the reactions of diazomethane with $\gamma$-phenyltetronic acid and with $\gamma\gamma$-diphenyltetronic acid, although in the latter
case a small inflection at 2570 Å (log $\varepsilon = 3.0$) might indicate the presence of a small amount of either unreacted tetronic acid or an ether of the keten-acetal type obtained with $\alpha$-methyltetronic acid.

The evidence now available, then, shows that the silver salt of $\alpha$-methyltetronic acid reacts with alkyl halides in benzene to give a higher proportion of O-alkylation the greater the hyperconjugation of the alkyl group. This is in accord with the theory of Kornblum mentioned in the introduction (p. 37), but steric effects are probably partly responsible.

The reaction of the sodium tetronates is more difficult to understand, since by comparison with acetoacetic ester and in accord with Kornblum's theory one might expect the sodium salts, if they reacted at all, to give only O-alkylation. Freer and Kumler (see introduction) found that the sodium salt of $\alpha$-methyltetronic acid underwent no alkylation, but in our experiments enol ethers were obtained in quite high yields using the sodium salts in polar solvents. It seems that in the $\alpha$-monoalkyl tetric acids without a polar solvent either solubility is too low or the carbonium content of the transition state is insufficient for alkylation to occur at any point in the molecule unless the silver ion is used, which gives stronger electrophilic attack on the halogen of the alkyl halide. The silver salt undergoes both C- and O-alkylation in a ratio determined by the hyperconjugation of the alkyl group. However, the sodium salts of tetronic acids can undergo alkylation in polar solvents, and the transition
state presumably has sufficiently high carbonium content for completely SN1 mode of reaction leading to O-alkylation. The SN1 character of the transition state is also due in part to the use of a polar solvent, since phenolates for example undergo O-alkylation in alcohol solution but C-alkylation in benzene solution.

It seems established, at any rate, that alkylation can occur of the tetronic acid nucleus corresponding to the three resonating forms of the anion (VII, VIII, IX) (see p. 32) although the form arising from form IX will receive further discussion. We can only explain these results in one of the three following ways:

1. The ion exists in only one form bearing the charge on the oxygen atom; this reacts with formation of the O-alkyl compound, which then either re-arranges into the C-alkyl compound or is hydrolysed. There is no evidence in support of such a re-arrangement giving C-alkylation except where it involves an allyl group (see Section III).

2. In the reaction mixture the metallic tetronates are present as both C-salts and ionisable O-salts in quantitative ratios dependent on the nature of the metallic ion and of the solvent agent. The C-salt and the anions of the O-salts react with methyl iodide in a ratio depending on the nature of the solvent, and the C-salt in particular reacts more quickly the less strongly ionising the effect of the solvent.
3. Only the ion reacts, but in all its conceivable forms.

On the basis of experimental results, it is not yet certain which mechanism is operative.

In fact it is not necessary to postulate the existence of the anion of type IX if we accept the mechanism proposed by Arndt ("Organic Analysis", Interscience Publishers, Inc., New York, Vol. I, p. 197; Arndt et al., Ber., 1938, 71, 1628; 1951, 84, 163, 745, 343) who regards the methylation process by diazomethane as one of attack not on the anion left after migration of the proton but on the acidic hydroxyl itself by a methylene group. This would still necessitate a contribution by the undissociated form giving rise to (IX), but would explain the fact that only O-alkylation occurs with diazomethane and tetronic acids.

The I.R. spectra of the ethers of tetronic acids are more easily interpreted than those of free tetronic acids. Many of the ethers have sufficiently low melting-points to permit the pure liquids to be used without Nujol or hexachlorobutadiene. The bands obtained (weak, medium or strong as indicated) for some neutral tetronic acid derivatives are tabulated.

(1) and (2) represent respectively authentic $\alpha\alpha'$-dimethyle- and $\alpha\alpha'$-diethyltetronic acids ([αα-dialkyl-β-oxobutyrolactones]. Superposable on (1) was the I.R. spectrum of the C-methylation product from silver $\alpha$-methyltetronate. (3) represents the low b.p. fraction of the product of ethylation of silver $\alpha$-methyltetronate, and is comparable to (1) and (2). (4) represents the normal enol methyl ether of $\alpha$-methyltetronic acid, prepared both by means of diazomethane and by silver salt-methylation; the spectra were identical except for the peak at 1608 cm$^{-1}$, which was slightly stronger for the product from the silver salt. The higher boiling fraction of the product of ethylation of silver $\alpha$-methyltetronate is represented in (5) which is more comparable to (4) in the carbonyl region than to (1) and (2). (6) represents the allyl ether of $\beta\alpha$-dimethyltetronic acid while (7) represents the solid methyl ether of $\alpha$-methyltetronic acid prepared by means of diazomethane.

It can be seen that only the saturated lactones (spectra (1), (2) and (3)) have bands in the region 1800 - 1810 cm$^{-1}$. 
These may represent the $\beta$-carbonyl group, but the increase in the carbonyl stretching frequency over the normal is greater than is usual in five- and six-membered rings. (Hartwell, Richards and Thompson, J., 1948, 1436, give $172 \text{cm}^{-1}$ for cyclopentanone.)

The carbonyl bands due to the $\beta$-unsaturated $\gamma$-lactonic groups (spectra (4), (5) and (6)) are at the expected frequencies (Grove and Willis, J., 1951, 877, give $1750 \text{cm}^{-1}$) at $1748 \text{cm}^{-1}$, $1754 \text{cm}^{-1}$ and $1767 \text{cm}^{-1}$. The saturated $\beta$-ketonic lactones show rather higher lactonic carbonyl frequencies ($1756 \text{cm}^{-1}$, $1760 \text{cm}^{-1}$ and $1767 \text{cm}^{-1}$) comparable to the normal $1770 \text{cm}^{-1}$.

Spectrum (7) shows no band in this region, and it alone shows a strong band at $1567 \text{cm}^{-1}$ ($6.4\mu\lambda$). This can be compared to the higher-frequency band reported by McElvaine and Starn (J. Amer. Chem. Soc., 1955, 77, 4576) for keten-acetals.

These compounds show two characteristic bands in the $6\mu$ ($1667 \text{cm}^{-1}$) and $10\mu$ ($1000 \text{cm}^{-1}$) regions. The lower frequency band is normally weaker and in spectrum (7) is less easily distinguishable. Kende (loc. cit.) reports the compound (1) as showing the characteristic band in the $6\mu$ region.

![Diagram](image-url)
<table>
<thead>
<tr>
<th>System</th>
<th>(1)</th>
<th>(2)</th>
<th>(3)</th>
<th>(4)</th>
<th>(5)</th>
<th>(6)</th>
<th>(7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$-\text{OH}$</td>
<td>(3575w)</td>
<td>(3563w)</td>
<td>3608w</td>
<td>3520w</td>
<td>3572m</td>
<td>3500w</td>
<td>3389w</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>3120w</td>
<td>3176w</td>
</tr>
<tr>
<td>$\text{CH}_3\text{CH}_2\text{C}=\text{O}$</td>
<td>2998m</td>
<td>2990m</td>
<td>2977m</td>
<td>2975w</td>
<td>2977w</td>
<td>2998s</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>2950m</td>
<td>2953m</td>
<td>2922w</td>
<td>-</td>
<td>2915w</td>
<td>2950s</td>
<td>2957m</td>
</tr>
<tr>
<td></td>
<td>2895w</td>
<td>2900w</td>
<td>-</td>
<td>2895w</td>
<td>-</td>
<td>2880m</td>
<td>2880m</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2760m</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2728m</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2578w</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2320w</td>
</tr>
<tr>
<td>$\text{C}=\text{O}$</td>
<td>1813m</td>
<td>1800m</td>
<td>1809m</td>
<td>-</td>
<td>-</td>
<td>1832m</td>
<td>-</td>
</tr>
<tr>
<td>lactonic</td>
<td>1760s</td>
<td>1756s</td>
<td>1767s</td>
<td>1754s</td>
<td>1767s</td>
<td>1748s</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>1709m</td>
<td>1700w</td>
<td>-</td>
<td>1717w</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>(1677w)</td>
<td>1674s</td>
<td>1679s</td>
<td>1630s</td>
<td>1690m</td>
</tr>
<tr>
<td>$-\text{C}=\text{O}$-stretching</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1607m</td>
<td>1608s</td>
<td>1603m</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>1607m</td>
<td>1608s</td>
<td>1603m</td>
<td>-</td>
</tr>
<tr>
<td>$\text{CH}_2\text{CH}_2\text{C}=\text{CH}_3$</td>
<td>1465m</td>
<td>1465m</td>
<td>1459m</td>
<td>1463m</td>
<td>1456m</td>
<td>1462s</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1437m</td>
<td>1446m</td>
<td>1442m</td>
<td>-</td>
<td>1424s</td>
<td>1430s</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1392m</td>
<td>1392w</td>
<td>1396w</td>
<td>1396s</td>
<td>1406s</td>
<td>1392s</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>1358w</td>
<td>1383w</td>
<td>1371m</td>
<td>1378m</td>
<td>1369s</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1363m</td>
<td>-</td>
</tr>
<tr>
<td>$\text{O}=\text{O}$-</td>
<td>1341m</td>
<td>1350w</td>
<td>1346m</td>
<td>1333s</td>
<td>1341s</td>
<td>1340s</td>
<td>1347w</td>
</tr>
<tr>
<td></td>
<td>1296s</td>
<td>(1300w)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$\text{O}=\text{O}$-</td>
<td>(1250w)</td>
<td>1242m</td>
<td>1262m</td>
<td>1258w</td>
<td>1259m</td>
<td>1258s</td>
<td>1267w</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1238w</td>
<td>1220w</td>
<td>1228w</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1214w</td>
<td>1196w</td>
<td>1205w</td>
<td>-</td>
<td>1200s</td>
<td>1205w</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1183w</td>
<td>1148s</td>
<td>-</td>
<td>1177w</td>
</tr>
<tr>
<td>System</td>
<td>(1)</td>
<td>(2)</td>
<td>(3)</td>
<td>(4)</td>
<td>(5)</td>
<td>(6)</td>
<td>(7)</td>
</tr>
<tr>
<td>----------</td>
<td>------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>C-CH₃ or ester gp.</td>
<td>1133s</td>
<td>1129m</td>
<td>1122m</td>
<td>1133m</td>
<td>-</td>
<td>1120s</td>
<td>1139m</td>
</tr>
<tr>
<td></td>
<td>1083s</td>
<td>1083m</td>
<td>1090m</td>
<td>1065s</td>
<td>1082s</td>
<td>-</td>
<td>1089w</td>
</tr>
<tr>
<td></td>
<td>1049s</td>
<td>1050s</td>
<td>1052s</td>
<td>1050s</td>
<td>1062s</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>1026w</td>
<td>-</td>
<td>1030s</td>
<td>-</td>
<td>998w</td>
</tr>
<tr>
<td></td>
<td>(966w)</td>
<td>-</td>
<td>965w</td>
<td>991m</td>
<td>961m</td>
<td>980s</td>
<td>973m</td>
</tr>
<tr>
<td>C-CH₂</td>
<td>(925w)</td>
<td>930w</td>
<td>-</td>
<td>-</td>
<td>932w</td>
<td>939s</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>825w</td>
<td>-</td>
<td>861w</td>
<td>892m</td>
<td>-</td>
<td>-</td>
<td>887m</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>802w</td>
<td>-</td>
<td>-</td>
<td>790m</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>750w</td>
<td>-</td>
<td>772w</td>
<td>758m</td>
<td>758m</td>
<td>(774m)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>708w</td>
<td>695w</td>
<td>697w</td>
<td>-</td>
<td>698w</td>
<td>-</td>
<td>681w</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>670w</td>
<td>680m</td>
<td>681w</td>
</tr>
</tbody>
</table>
**EXPERIMENTAL DETAILS.**

**Methylation by Diazomethane.**

(i) **Diazomethane.**

This was prepared by the method of de Boer and Backer (Rec. Trav. chim. 1954, 73, 229) from p-tolylsulphonylmethyl-nitrosoamide.

(ii) **Methylation of χ-phenyltetronic acid.**

To a suspension of χ-phenyltetronic acid (8.8 g., 0.05 mol.) in dry ether (150 ml.) was added slowly a dry ethereal solution (100 ml.) of diazomethane (3.2 g., approx., 0.075 mol.). Nitrogen was immediately evolved and the solution was set aside overnight. The excess of diazomethane was then expelled by gentle heating and some white solid (0.5 g., m.p. >300°, probably polymethylene) was collected by filtration and rejected.

Evaporation of the ether at reduced pressure left a yellow oil (9.9 g.) which even after standing for several weeks gave no effervescence with aqueous sodium bicarbonate and gave a negative nitrite test. When run on a paper chromatogram with solvent system (ix) (see section on Chromatography) the impure oil ran completely at the solvent front with no indication of free acid. The methyl ether crystallised as long rods from ethyl acetate/light petroleum (b. 60 - 80°), m.p. 96 - 97°. (Raphael, J., 1949, 118, gives m.p. 98°).

(iii) **Methylation of χχ-diphenyltetronic acid.**

To a suspension of χχ-diphenyltetronic acid (5.0 g., 0.02 mol.) in dry ether (100 ml.) was added a solution of diazomethane
(about 1.1 g., 0.025 mol.) in dry ether (50 ml.) and the solution set aside overnight. Polymethylene (0.3 g.) was removed, the ether solution was washed with aqueous sodium hydrogen carbonate, dried (Na₂SO₄) and ether removed at reduced pressure. The solid residue was recrystallised from methanol to give pure

\[ \gamma \]-diphenyltetronic acid methyl ether (3.2 g., 60%), m.p. 161 - 163°C. Mixed m.p. with product of dimethyl sulphate method, 161 - 163°C; U.V. absorption spectrum identical also.


To a suspension of \( \alpha \)-methyltetronic acid (11.4 g., 0.1 mol.) in dry ether (200 ml.) was slowly added a solution of diazomethane (6.3 g. approx., 0.15 mol.) in ether (200 ml.). Nitrogen was evolved and the mixture was set aside overnight. Polymethylene (0.6 g.) was removed and the filtrate distilled at reduced pressure. A colourless solid accumulated in the condenser, while a colourless distillate (b. 84 - 95°C/0.05 mm., 5.2 g., 41%) was collected and microfractionated to give 3 fractions:

\[ \begin{align*}
a) & \quad 82^0/0.03 \text{ mm.}, m^3 1.4920. \\
b) & \quad 84^0/ \quad \ldots \quad 1.4948. \\
c) & \quad 84^0/ \quad \ldots \quad 1.4930. \\
\end{align*} \]

(Calow, Todd and Waring, *Biochem. J.*, 1949, 45, 522, give 160 - 170°C/15 mm.).
I.R. absorption spectra were obtained for fractions (a) and (c), showing both to be identical to the \( \alpha \)-methyltetronic acid methyl ether obtained by methylation of the silver salt with methyl iodide.

The solid product, which sublimed readily, was recrystallised four times, from dry ether as long needles, m.p. 79 - 81°C (Stodola et al., loc. cit., give m.p. 84 - 85°C). (Found: C, 54.91; H, 6.18. Calc. for \( \text{C}_6\text{H}_8\text{O}_3 \): C, 56.26; H, 6.29%). I.R. absorption spectra were obtained. The substance gave a purple colour with aqueous sodium nitrite and on standing for some weeks gave impure \( \alpha \)-methyltetronic acid, m.p. 183 - 184°C (lit. m.p. 185 - 187°C).

A sample of the freshly-prepared solid product (0.5 g., dried in vacuo over \( \text{P}_2\text{O}_5 \)) was heated in the steam-bath for 1 hour with absolute ethanol (10 ml.), hydroxylamine hydrochloride (0.5 g.) and pyridine (0.5 ml.). The mixture was allowed to stand overnight and then was evaporated, giving a solid residue which was recrystallised from absolute ethanol to give a substance which was probably the oxime; decomp. 150°C approx., m.p. 325°C (pyridine hydrochloride m.p. 82°C; dihydrochloride m.p. 46°C).
Ethylation of \( \gamma\gamma \)-Diphenyltetronic Acid (with Mr. D. S. Allan).

A. **Using ethyl bromide:**

\( \gamma\gamma \)-Diphenyltetronic acid (5.0 g., 0.02 mol.) was dissolved in aqueous sodium hydroxide solution (30 ml. of 15%) and ethyl bromide (6.6 g., 0.06 mol.) added. No reaction occurred at room temperature and so a similar mixture was refluxed for 5 hours, cooled and extracted with ether. The ether extract was washed with aqueous sodium bicarbonate and water, dried \( \text{Na}_2\text{SO}_4 \) and evaporated. The residue (0.5 g., 9%) recrystallised from ethanol as pure \( \gamma\gamma \)-diphenyltetronic acid ethyl ether, m.p. 108 - 110\( ^\circ \). (Found: C, 76.75; H, 5.73. \( \text{C}_{18}\text{H}_{16}\text{O}_3 \) requires: C, 77.11; H, 5.71%).

Acidification of the alkaline layers precipitated unchanged tetronic acid. The U.V. absorption spectra of the ethyl ether in ethanol showed no distinct maximum above 2090 A \( (\log \varepsilon 4.3) \).

B. **Using diazomethane:**

(i) **Diazomethane** (cf. de Boer and Backer, loc. cit.).

To ethylamine (15.8 g., 0.35 mol.) was added p-toluenesulphonyl chloride (25 g., 0.13 mol.) during 4 minutes, while the mixture was shaken and the temperature kept below 70 - 90\( ^\circ \). When the mixture became acid, sodium hydroxide (5.6 g. in 12 ml. water) was added followed at once by p-toluenesulphonyl chloride (17 g., 0.09 mol.). When the mixture became acid once more, sodium hydroxide (4.6 g. in 10 ml. water) followed by p-toluenesulphonyl chloride
(11 g., 0.06 mol.) was added. The solution was then alkaline.

The mixture was stirred and heated on a boiling water-bath for 0.25 hour, and then poured into acetic acid (250 ml.) and the flask washed with acetic acid (60 ml.).

The solution of p-toluenesulphonyl-ethylamide was stirred and cooled to 0 - 5° while a solution of sodium nitrite (21 g., 0.36 mol.) in water (45 ml.) was added dropwise during 0.5 hour. The nitroso-compound separated as an oil which solidified on standing. Stirring was continued for 0.25 hour and then water (250 ml.) was added. The nitrosamide was collected by filtration and washed free of acetic acid, and dried in vacuo over conc. H₂SO₄. M.p. 35 - 37°. Yield 55 g. (86%).

The method detailed for the preparation of diazomethane by de Boer and Backer (loc. cit.) was followed, using p-tolylsulphonyl-ethyl-nitrosamide (16 g., 0.07 mol.) and potassium hydroxide (5 g., 0.09 mol.).

(ii) Ethylation.

A solution of diazoethane (about 1.4 g., 0.025 mol.) in dry ether (70 ml.) was added to a suspension of p-diphenyltetronic acid (5.0 g., 0.02 mol.) in dry ether (100 ml.). Nitrogen was evolved, and the yellow solution was set aside overnight when it had become deep red.

A little crystalline material was removed by filtration (unchanged acid, 0.5 g.) and the ether solution was washed
with aqueous bicarbonate solution, acidification of which gave no precipitate. The ether solution was dried (Na₂SO₄) and solvent removed at reduced pressure leaving a red resin. Attempts to decolourise and to crystallise this solid failed.

The solid gave a blue colour with aqueous sodium nitrite and dissolved in aqueous sodium hydrogen carbonate, acidification of the solution, giving \( \text{diphenyltetronic} \) acid (m.p. 210°).

A second attempt at ethylation was carried out, using \( \text{diphenyltetronic} \) acid and diazoethane in the same amounts as before. The yellow ether solution was allowed to stand for only 1 hour, when a pale yellow non-crystalline material (1.9 g.) was collected by filtration and stored in a desiccator. Solvent was removed from the ethereal solution leaving an oil which was treated with a little dry ether. The solid which resulted was collected by filtration but almost at once became like the first solid product. Both were hygroscopic although remaining quite solid in the desiccator; both gave positive nitrite tests and were soluble in aqueous sodium bicarbonate solution, acidification giving normal \( \text{diphenyltetronic} \) acid. No exact m.p. could be determined (over 100°).

The product was found to contain no nitrogen. Its U.V. absorption spectrum showed 1 maximum at 2570 Å (εₚₐₓ = 12,620). This may be compared to the spectra of
\(\gamma\gamma\)-diphenyltetronic acid, with \(\lambda_{\text{max}} = 2580 \text{ Å}, \varepsilon_{\text{max}} = 15,800\), and of compound I for which Kende (loc. cit.) gives m.p. 125 - 126° and \(\lambda_{\text{max}} = 2560 \text{ Å}, \varepsilon_{\text{max}} = 13,800\).

\[\text{I}\]

**Alkylation by the Silver Salt Method.**

(1) **Allyl ether of 6-methylpyronone.** (cf. Sproston, J., 1906, 1186)

A concentrated aqueous solution of 6-methylpyronone (12.6 g., 0.1 mol.) prepared from dehydracetic acid by the method of Collie (J., 1891, 59, 607), was neutralised with concentrated ammonia solution and to the solution of the ammonium salt so formed excess saturated silver nitrate solution was added. The precipitated silver salt (18.4 g., 79%) was collected and dried in a desiccator.

The dry silver salt (18.4 g., 0.079 mol.) was suspended in dry ethanol (200 ml.) and allyl bromide (20 g., 0.165 mol.) was added. The mixture was heated under reflux in a water-bath for 3.5 hours, silver bromide (14.2 g.) was removed by filtration and the solvent was removed by distillation under reduced pressure. A dark red sweet-smelling oil (7.7 g.) remained, which gave a red colour with aqueous ferric chloride. The oil was stirred with aqueous sodium bicarbonate solution,
the suspension was extracted with chloroform, the chloroform extract was dried (Na$_2$SO$_4$) and solvent was removed under reduced pressure. The residue was crystallised from ethyl acetate to give the 6-methylpyronone allyl ether, m.p. 158° (3.2 g., 32%). (Found: C, 65.21; H, 6.01. C$_9$H$_{10}$O$_3$ requires: C, 65.04; H, 6.06%). Its U.V. absorption spectra in ethanol showed one maximum at 2890 Å, log ε 4.0.

Williamson's method gave only poor yields of the same allyl ether.

(ii) Methyl ether of α-methyltetronic acid (Conrad and Gast, Ber., 1898, 31, 2731).

The procedure of Conrad and Gast and of A. H. Stanners (Ph. D. Thesis, Edin. 1956, 41) was repeated with similar results to those obtained by Stanners. Fractionation of the product gave two substances in a ratio of 1:2, b.p. 49 - 50°/0.2 mm. (m.p. 14° approx.) and b.p. 52 - 56°/0.3 mm. respectively, with distinct I.R. absorption spectra. The second product gave an oxime m.p. 132 - 133°; the first product would not form an oxime.

**Authentic d,l-dimethyl-β-oxobutyrolactone.**

This was prepared by acetylation of ethyl 1-bromo-d,l-dimethylacetoacetate followed by cyclisation in conc. sulphuric acid (Reid, Fortenbaugh and Patterson, J. Org. Chem., 1950, 15, 572). Ethyl α-methyl- and d,l-dimethylacetoacetates were prepared according to the
The monomethyl ester was prepared using sodium (39.8 g.,
1.73 g. atom), ethyl acetoacetate (218.3 g., 1.68 mol.), and
methyl iodide (253 g., 1.73 mol.). The dimethyl ester was
then prepared by a similar procedure using sodium (35.6 g.,
1.55 g. atom), ethyl L-methylacetoacetate (216 g., 1.50 mol.),
and methyl iodide (227 g., 1.6 mol.). The sodium was first
powdered to the consistency of sand, the xylene was decanted,
and the sodium was washed with dry toluene (2 x 75 ml.). The
sodium was then covered with dry toluene (1 l.) and the flask
was fitted with a reflux condenser, immersed in an ice-bath,
and allowed to cool for 15 minutes, after which the ester was
added down the condenser during the course of 10 - 15 minutes
while the flask was vigorously shaken and kept in an ice-bath.
The top of the condenser was fitted with a CaCl₂ guard-tube
and after 10 minutes' further cooling the mixture was allowed
to stand at room temperature for 10 hours with occasional
vigorous shaking during the first hour. The reflux condenser
was then temporarily removed, a long-stemmed funnel was
pushed down into the semi-solid salt, and the methyl iodide
was added.

After standing overnight the flask was heated for 14
hours on the steam-bath with vigorous shaking every other
hour. The sodium had then settled out completely and was
removed by filtration and pressed dry with suction. The
filtrate was then fractionally distilled under reduced pressure
through a 25 cm. Penske column. To ensure complete
dimethylation the second distillate was added to sodium
(2.5 g.) in dry toluene and placed under reflux-condenser,
and allowed to stand for 5 hours, when methyl iodide (7 g.)
was added. The mixture was allowed to stand overnight and
then heated for 0.5 hour on the steam-bath. The sodium
iodide was removed by filtration and the toluene and ester
fractionally distilled through a Penske column.
Yields: of the monomethylacetoacetate 166 g. (68%)
b.p. 75 - 76°/15 mm.; of the dimethylacetoacetate 120 g.
(51%) b.p. 72 - 73°/14 mm. (yellow-grey colour with neutral
ferric chloride).

Ethyl \(\gamma\)-bromo-\(\alpha\)-dimethylacetoacetate (G. Conrad, Ber.,
1897, 30, 856; Conrad and Gast, Ber., 1898,
31, 2728).

Bromine (48 g., 0.30 mol.) was added dropwise during
6 hours to an ice-cooled mixture of ethyl \(\alpha\)-dimethylacetoacetate
(47 g., 0.30 mol.) and dry ether (45 ml.). When the mixture
had stood overnight it was diluted with ether (150 ml.),
washed several times with water, dried (Na2SO₄) and solvent
removed. The crude bromo-compound, a brown oil, was used
in the next stage without purification.

Acetalysis.

Crude ethyl \(\alpha\)-dimethyl-\(\gamma\)-bromoacetoacetate (55 g.,
0.23 mol.) was dissolved in an equal volume of ethanol and
mixed with a solution of anhydrous potassium acetate
(45 g., 0.46 mol.) in absolute ethanol (300 ml.). The mixture was heated for 2 hours on a water-bath under reflux. Potassium bromide (21 g., 0.18 mol.) separated and when cool the mixture was filtered. Water (600 ml.) was added and the mixture was extracted with ether, the extract was dried (Na₂SO₄) and ether removed, leaving a brown liquid. To ensure complete acetylation this was treated as before with more potassium acetate, and more potassium bromide (4 g.) separated. The liquid obtained (40 g., 78%) was used in the next stage without distillation. 

\[\text{D}-\text{Dimethyl-} \beta\text{-exobutyrolactone} \] (Conrad and Gast, loc. cit.; Reid, Fortenbaugh and Patterson, loc. cit.)

Crude ethyl \( \gamma \)-acetoxy-\( \text{D} \)-dimethylacetooctetate (40 g., 0.18 mol. was added slowly to conc. sulphuric acid (150 g.) with cooling during 0.5 hour. The dark brown mixture was kept for 48 hours in a closed container at 0°, and was then poured on to ice (400 g.) and allowed to reach room temperature and stand for 2 hours more. The mixture was extracted thoroughly with chloroform, the extract washed free of sulphuric acid with aqueous sodium hydrogen carbonate and water, dried (Na₂SO₄) and distilled under reduced pressure. A considerable dark brown residue remained from the distillation. The fraction with b.p. 41 - 42°/0.07 mm., \( n_D^{17} 1.4543 \) (10.5 g., 44%) was collected. From it the oxime was prepared using the acid (0.5 g.), hydroxylamine hydrochloride (0.5 g.), ethanol (5 ml.) and pyridine (0.5 ml.) refluxed for 20 minutes in a water-bath. Solvent was removed and water (5 ml.) added, when the oxime
crystallised at once. Recrystallised twice from ethanol it had m.p. 132 - 134° (subliming). (Reid et al., loc. cit., give m.p. 132 - 134°.) The I.R. absorption spectrum was obtained.

The m.p. of a mixture of the authentic oxime and the oxime from the C-methylation product was 132 - 134°.

(iii) Ethyl ether of \( \alpha \)-methyltetronic acid (Cf. Freer, Amer. Chem. J., 1894, 13, 313; idem. ibid., 1895, 17, 795). Silver \( \alpha \)-methyltetronate (11.1 g., 0.05 mol.) and dry A.R. benzene (150 ml.) were placed in a 500 ml. flask fitted with a mercury-sealed stirrer, dropping-funnel and reflux condenser (guard-tubes), and lagged to exclude light. The mixture was gently refluxed on the steam-bath and ethyl iodide (11.7 g., 0.075 mol.) introduced dropwise during 1 hour. The heating was continued for 15 hours further and then the mixture was cooled and the precipitate of silver iodide (9.8 g.) filtered off and washed with ether. The introduction of the ether into the benzene solution produced a turbidity.

The bulk of the ether and benzene was removed under reduced pressure, the residue was dissolved in ether and the solution washed with saturated aqueous sodium hydrogen carbonate. The ethereal solution was dried (\( \text{Na}_2\text{SO}_4 \)) and
distilled at reduced pressure. Five fractions of distillate were collected (Cf. Freer, loc. cit., who isolated two products from the reaction of silver \(\alpha\)-methylltetronate and ethyl iodide in a sealed tube, b.p. 175 - 176°/50 mm., and 180°/43 mm., m.p. 28° resp.):—

\[\begin{array}{lll}
a) & 54°/0.05 mm., 0.8 g., n^D_4 1.4609 & \\
b) & 57 - 67°/0.03 mm., 0.6 g., n^D_4 1.4599 & \\
c) & 67 - 72°/0.03 mm., 0.6 g., n^D_4 1.4737 & \\
d) & 85 - 87°/0.03 mm., 2.0 g., n^D_4 1.4865 & \\
e) & 87°/0.03 mm., 0.7 g., n^D_4 1.4850 & \\
\end{array}\]

Higher-boiling residue, 2.2 g.

The last two fractions crystallised slowly and would not form an oxime. Fractions (a) and (d) had different I.R. absorption spectra. Fractions (a) and (b) formed an oxime as follows:

Fraction (a)(0.5 g.) was dissolved in absolute ethanol (5 ml.) and hydroxylamine hydrochloride (0.5 g.) and pyridine (0.5 ml.) were added. The mixture was heated under reflux in a steam-bath for 0.5 hour. Evaporation at reduced pressure left a crystalline residue which crystallised from absolute ethanol as needles m.p. 154° (subliming) of the oxime of \(\alpha\)-methyl-\(\alpha\)-ethyl-\(\beta\)-oxobutyrolactone. (Found: C, 54.01; H, 7.14. \(\text{C}_7\text{H}_{11}\text{O}_2\text{N}\) requires: C, 53.48; H, 7.05%).

(iv) \(\beta\)-Butyl ether of \(\alpha\)-methylltetronic acid.

A similar experiment using silver \(\alpha\)-methylltetronate (11.1 g., 0.05 mol.) and \(\beta\)-butyl iodide (13.8 g., 0.075 mol.) was carried out. The suspension in benzene was heated for
18 hours on a steam bath, cooled and filtered. Removal of benzene at reduced pressure left an oil with a small amount of crystalline material, which was heated in benzene with charcoal for 10 minutes. The mixture was cooled, filtered, and solvent was removed at reduced pressure. A semicrystalline material (2.1 g., 21.6%) remained which showed signs of crystallising in ethyl acetate, but no crystals could be separated. Attempts to prepare ketonic derivatives were unsuccessful. The substance was "short-path distilled" at 100°/1 mm. The semicrystalline distillate showed $\lambda_{\text{max}}$, 2490 $\AA$, log $\varepsilon$ 4.92, with a slight inflection at 2980 $\AA$, log $\varepsilon$ 3.48; further attempts to prepare ketonic derivatives were unsuccessful.

**Alkylation by Dimethyl Sulphate; Stability to Hydrolysis**

(with Mr. N. M. Philip).

Using the following procedure the ethers of some tetronic acids were prepared and their stability to alkaline hydrolysis determined. The tetronic acid was dissolved in a small excess of sodium hydroxide solution (15% aqueous) in a 3-necked flask fitted with a stirrer, condenser and dropping-funnel. The solution was stirred vigorously and dimethyl sulphate (50% molar excess) was added dropwise. The mixture was stirred at room temperature for 4 hours and extracted with ether. The ether extract was washed with saturated aqueous sodium hydrogen carbonate, dried and evaporated.
at reduced pressure. The ethers of \( \alpha \)-methyltetronic acid (53\%, b.p. 42 - 44\(^\circ\)/0.1 mm.), \( \gamma \)-phenyltetronic acid (74\%, b.p. 69\(^\circ\)/11 mm.) and \( \gamma \)-dimethyltetronic acid (78\%, b.p. 76 - 77\(^\circ\)/11 mm.) were obtained by distilling the residue. The ethers of \( \gamma \)-spirocyclohexyltetronic acid (66\%) and \( \gamma \gamma \)-diphenyltetronic acid (75\%, m.p. 162\(^\circ\)) from methanol.

Found: C, 76.99; H, 5.16. C\(_{17}\)H\(_{14}\)O\(_3\) requires C, 76.69; H, 5.26\%.) were obtained by recrystallising the residue.

\( \gamma \gamma \)-Diphenyltetronic acid methyl ether in ethanol showed log \( \varepsilon \) 4.2 at 2150 \( \lambda \).

A weighed quantity of the ether (0.5 - 1.0 g.) was added to an approximately 1 \( \overline{\text{N}} \) standardised solution (20 ml.) of sodium hydroxide in a standard flask and the solution was diluted to 100 ml. with water and the minimum of ethanol to give solution of the ether. Portions of 10 ml. were withdrawn at intervals of several hours and back-titrated with standard hydrochloric acid to determine the amount of sodium hydroxide neutralised. In this way the ethers of \( \gamma \)-spirocyclohexyltetronic acid (crude) and of \( \gamma \gamma \)-diphenyltetronic acid were shown to be unchanged by standing with sodium hydroxide for 24 hours, while the methyl ethers of \( \alpha \)-methyltetronic, \( \gamma \)-phenyltetronic and \( \gamma \gamma \)-dimethyltetronic acids neutralised 1 equivalent of NaOH in 1 hour at room temperature. The products of the last two hydrolysers were shown chromatographically by solvent system (ix)(see Section III) to be respectively \( \gamma \)-phenyl- and \( \gamma \gamma \)-dimethyltetronic acids.
SECTION XIII

THE AROMATIC PROPERTIES OF TETRONIC ACIDS
INTRODUCTION

Reports in literature on the reactions of tetronic acids have been confined for the most part to descriptions of electrophilic substitution reactions, such as nitration, sulphonation, halogenation, and coupling with diazonium salts. Other reactions normally associated with phenolic compounds have been investigated to extend the comparison.

Molecular re-arrangements of the Fries or Claisen type have not been reported in the tetronic acid series. In the aromatic series, allyl aryl ethers can be induced to re-arrange to give allyl phenols (the "Claisen" re-arrangement) while esters of phenols in presence of Friedel-Crafts catalysts react to give ketonic derivatives of the phenols (the "Fries" re-arrangement).

The Fries reaction would provide a new route to \( \alpha \)-acyltetronic acids and moreover might conceivably provide a means of introducing the ketonic \( \alpha \)-substituent groups possessed by several naturally occurring tetronic acid derivatives - carollc, caralic, carolinic, carlosic and terrestric acids (see General Introduction). Carolinic acid, for example, has the nucleus of \( \delta \)-methyltetronic acid with a \( \beta \)-carboxypropionyl group in the \( \alpha \)-position, and perfection of the acylation either by direct attack or by re-arrangement, could lead to a synthesis by way of I. The analogous monoarylsuccinates undergo re-arrangements of the Fries type.
in presence of aluminium chloride to give

\[ \beta \text{-aroylpropionic acids (Awad et al., J., 1954, 4538).} \]

\[
\begin{align*}
\text{Me} & \quad \text{O} \\
\text{OOC\{CH}_2\text{\}_2\text{COOH}} & \\
\end{align*}
\]

I

It was decided therefore to subject appropriate tetronic acid derivatives to conditions suitable for Fries and Claisen re-arrangements, and also to attempt to carry out other reactions usually associated with aromatic phenols. Normal Friedel-Crafts techniques might give direct substitution in the \( \alpha \)-position of the tetronic acids, leading to the same \( \alpha \)-acyl derivatives as the Fries re-arrangements, while \( \alpha \)-acetyltetronic acids might also be obtained by a Hoesch reaction. The Houben-Hoesch synthesis normally consists in the condensation of a nitrile with a phenol, a polyhydric phenol or a phenolic ether to form a hydroxyaryl or alkoxyaryl ketone.

\( \gamma \)-Phenyltetronic acid was chosen for the early investigations into these reactions for a number of reasons. Not only is it readily prepared, but the monophenyl \( \gamma \)-substituent gives it and its \( \alpha \)-derivatives low solubility in cold water so that they can readily be recovered.
It was first ascertained that \( \gamma \)-phenyltetronic acid did in fact undergo the substitution reactions reported for tetronic acid itself. The method of Wolff and his co-workers for nitration (Ann., 1900, 312, 165 and 133) using nitric acid in warm glacial acetic acid, when applied to \( \gamma \)-phenyltetronic acid gave \( \alpha \)-nitro-\( \gamma \)-phenyltetronic acid in 52% yield which crystallised as needles (m.p. 110°) from light petroleum and gave no colour with aqueous sodium nitrite solution. The absorption spectrum (\( \lambda_{\text{max}} \), 2500 \( \AA \), \( \log E \approx 3.8 \)) was comparable with that of \( \gamma \)-phenyltetronic acid itself (\( \lambda_{\text{max}} \), 2520 \( \AA \), \( \log E \approx 4.2 \)) in ethanol.

Wolff's method of bromination (Ann., 1896, 221, 231) was also applied to \( \gamma \)-phenyltetronic acid. Dibromination, which Wolff attributed to traces of moisture or excess bromine, was brought about by using a 25% excess of bromine. Two products were obtained and separated by means of sodium bicarbonate. The neutral dibromo-\( \gamma \)-phenyl-\( \beta \)-exobutyrolactone, crystallised from light petroleum, gave a negative nitrite test and showed \( \lambda_{\text{max}} \), 2680 \( \AA \), \( \log E \approx 3.6 \). The acid dibromo-\( \gamma \)-phenyltetronic acid, crystallised from ethyl acetate/light petroleum, gave a positive nitrite test and had an absorption spectrum comparable to that of \( \gamma \)-phenyltetronic acid (\( \lambda_{\text{max}} \), 2540 \( \AA \), \( \log E \approx 4.0 \)).

\( \gamma \)-Phenyltetronic acid was also shown to undergo diazo-coupling in potassium carbonate solution (cf. Wolff and Lüttringhaus, Ann., 1900, 312, 133) to give dibenzeneazo-\( \gamma \)-phenyltetronic acid. This had \( \lambda_{\text{max}} \), 3560 \( \AA \), \( \log E \approx 3.5 \), with an inflection at 2840 \( \AA \), \( \log E \approx 3.9 \).
Having shown that \( \gamma \)-phenyltetronic acid possessed the properties which characterise tetronic acid itself, we then turned to the investigation of the Friedel-Crafts, Fries, Hoesch, Grignard and Claisen reactions.

Since the first three of these reactions in their simplest forms would lead to \( \alpha \)-acetyl-\( \gamma \)-phenyltetronic acid, a sample of this compound was needed for comparison purposes. This substance has been prepared by Lecocq \( (\text{Compt. rend.}, 1946, 222, 183) \) from \( \alpha \)-bromomandelyl chloride (I) and \( \beta \)-methylaminocrotonic ester (II), the N-methyl-\( \alpha \)-tetronamide (III) being hydrolysed to give the required product (IV).

\[
\begin{array}{c}
\text{Ph.CHBr.COOH} \\
\text{II}
\end{array}
\rightarrow
\begin{array}{c}
\text{Me} \\
\text{Ne} \\
\text{NHMe}
\end{array}
\begin{array}{c}
\text{I}
\end{array}
\rightarrow
\begin{array}{c}
\text{Me} \\
\text{O} \\
\text{NHMe}
\end{array}
\begin{array}{c}
\text{II}
\end{array}
\rightarrow
\begin{array}{c}
\text{Me} \\
\text{O} \\
\text{NHMe}
\end{array}
\begin{array}{c}
\text{III}
\end{array}
\rightarrow
\begin{array}{c}
\text{Me} \\
\text{O} \\
\text{NHMe}
\end{array}
\begin{array}{c}
\text{IV}
\end{array}

Lacey has also prepared it in 55% yield by cyclisation of methyl mandelylacetoacetate \( (J., 1951, 832) \).

It was more convenient, however, to use two other routes,
The first was analogous in its cyclisation by elimination of ethyl acetate to the method of preparing γ-phenyltetronic acid. Acetylmandelyl chloride (V) was condensed with ethyl sodioacetacetate to give a neutral oil which was probably the uncyclised product (VI). Several attempts were made to cause cyclisation in this condensation product by elimination of ethyl acetate. Neither refluxing with water or toluene for several hours, nor short-path distillation of the oil had any effect, but when it was brought into solution in 0.5N sodium hydroxide by the addition of the minimum of ethanol and allowed to stand for 24 hours cyclisation occurred. Acidification precipitated α-acetyl-γ-phenyltetronic acid which was recrystallised from light petroleum to analytical purity when it compared in m.p. and derivatives to the compound described by Lepoce (loc. cit.). From 0.02 molar scale the yield after four recrystallisations was about 26%. Poorer yields resulted from the use of a larger scale.

In the second route to α-acetyl-γ-phenyltetronic acid, α-acetimido-γ-phenyltetronic acid (VIII) was prepared according to the method used by Robstock and Sell (J. Amer. Chem. Soc., 1952, 74, 274) for α-acetimido-γ-methyltetronic acid. Acetylmandelyl chloride and ethyl β-aminocrotonate (VII) were condensed at -50° in presence of pyridine and the purified crystalline product hydrolysed easily. Alkaline hydrolysis (10% NaOH) at room temperature gave α-acetyl-γ-phenyltetronic acid in 48% yield; acid hydrolysis (2N HCl) at room temperature gave only 18% yield.
Ph₂CH₃COCl → Ph₂CH₃CO₂H → Ph₂CH₃CO₂Et

V

Ph₂CH₃CO₂ CH⁻Na⁺ → Ph₂CH₃CO₂CH⁻ CO₂Rt

VI

Ph₂CH₃CO₂H → Ph₂CH₃CO₂H

VII

Ph₂CH₃CO₂H → Ph₂CH₃CO₂H

VIII
By these two methods, then, neither of which gave an improvement in yield on existing methods, authentic \( \alpha \)-acetyl-\( \gamma \)-phenyltetronic acid was prepared and was shown to have the properties expected and already reported (loc. cit.) for this compound. It had \( \lambda_{\text{max}} \) 2650 \( \AA \) (\( \log \varepsilon \) 4.3) and 2320 \( \AA \) (\( \log \varepsilon \) 4.1) in neutral and alkaline solutions, with a minimum at 2440 \( \AA \). In ethanol containing some HCl it had no maximum at 2300 \( \AA \), which must have been associated with the tetronic acid anion. (Cf. \( \alpha \)-acetyl tetronic acid itself in water with \( \lambda_{\text{max}} \) 2650 \( \AA \) and 2300 \( \AA \), and \( \lambda_{\text{min}} \) 2430 \( \AA \); Herbert and Hirst, Biochem. J., 1935, 39, 1824).

**Development of Chromatographic Technique.**

Some means of following the substitution reactions and of estimating the extent to which they proceeded had to be devised which avoided the necessity of isolating the product. Paper-chromatographic technique seemed to be the solution to the problem, although some difficulty was experienced in finding a solvent system to separate \( \gamma \)-phenyltetronic acid from its authentic \( \alpha \)-acetyl derivative. Several systems were tried and discarded before the system used by Bray et al. (Biochem. J., 1950, 47, 13) for the separation of phenolic acids from the phenols and from each other in amounts of about 5/9 was found to be satisfactory. This solvent consisted of \( \gamma \)-butanol/pyridine/ammonia (0.880)/sat. aq. sodium chloride (40:80:30:50, v/v/v) and was found
to give separations of \( \gamma \)-phenyl-\( \beta \)-methyl-, \( \gamma \gamma \)-diphenyl-, \( \gamma \delta \)-dimethyl-, and \( \gamma \)-spirocyclohexyltetronic acids from their respective \( \alpha \)-acyl derivatives and from benzoic acid.

\( \alpha \)-Disubstituted tetronic acids and tetronic acid enol ethers were found to run at the solvent-front, but the enol esters ran as the respective separate anions. \( \alpha \)-Substitution was found in almost every case to increase the \( R_p \) value of the tetronic acid.

Development of the irrigated papers also presented some difficulty. Aqueous ferric chloride solution gives colours with many tetronic acids but not all; and the production of a yellow background decreases the sensitivity of the method for development purposes. \( \alpha \)-Substituted (except \( \alpha \)-bromo-) tetronic acids do not give the transient colours with aqueous sodium nitrite which the unsubstituted give. A method of development effective for all tetronic acid derivatives and adequately sensitive, proved to be by U.V. light absorption. Photographic printing paper was placed in contact behind the thoroughly dried chromatograms which were then exposed for 2 - 3 seconds to a Hanovia analytical lamp. Development of the photographic paper in the normal way showed the positions of the spots.

In the reactions next to be described, then, the practice adopted was to carry out the substitution or re-arrangement under varied conditions and to run the crude product on a
paper chromatogram against standards of the unsubstituted

tetronic acid, the authentic acetyletnetric acid if

available, and benzoic acid where appropriate. In this way

reaction conditions could be selected to give a crude product

containing the maximum proportion of the desired substitution

product.

**Friedel-Crafts Substitution.**

In the Friedel-Crafts acylation of phenols and other

aromatic compounds the aromatic component, acyl halide and

aluminium halide react to provide hydrogen halide and an

oxonium complex of aromatic ketone and aluminium halide

from which the ketone is obtained by addition to water or

dilute acid:—

\[ \text{ArH} + R,\text{COX} + \text{AlX}_3 \rightarrow \text{HX} + \text{Ar},\text{COR},\text{AlX}_3 \xrightarrow{\text{H}_2\text{O}} \text{Ar, COR} \]

Preliminary mixing of acyl and aluminium halides is

usually the best procedure, and the complexes so formed have

been named as the effective electrophilic reagents in the

Friedel-Crafts acylation reaction:—

\[ R,\text{CX} + \text{O}^+ \text{AlX}_3^- + \text{ArH} \rightarrow R,\text{CAR} = \text{O},\text{AlX}_3 + \text{HX} \]

Friedel-Crafts acylation thus differs from alkylation in that

it requires a molar quantity of AlX₃ with respect to the acyl

halide instead of just catalytic amounts. In the case of

phenols and AlCl₃ the molecular compounds ArO·AlCl₂ are formed
and so require an extra equivalent of catalyst. A process involving complete ionisation to give an acyl cation which would act as the electrophilic reagent has been suggested by Meerwein:

\[ R \cdot \text{CO}_2 \cdot X + \text{AlX}_3 \rightarrow R \cdot \text{CO}^+ + \text{AlX}_4^- \]

This theory is supported by the fact that halogen exchange has been shown to occur between acyl and aluminium halides. It is probable that in general acylation is effected by both the oxonium complex and the acyl cation.

ACYLATION REACTIONS AFFORD KETONE IN PROPORTION TO THE ALX₃ CATALYST USED (UNTIL ABOUT 1 MOL. EQUIVALENT HAS BEEN ADDED) BUT EXCESSIVE QUANTITIES OF CATALYST SHOULD BE AVOIDED TO MINIMISE UNDESIRABLE SIDE-REACTIONS. FOR THIS REASON PRELIMINARY MIXING OF THE AROMATIC REACTANT AND ALUMINIUM HALIDE IS AVOIDED, AND THE REACTION MIXTURE IS ADDED TO WATER AS SOON AS THE REQUIRED REACTION IS ESSENTIALLY COMPLETE.

The usual method for acetylation of phenols, then, employs nitrobenzene or carbon disulphide as solvent to which a small excess of the calculated amount of acetyl chloride is added followed gradually by a slight excess of AlCl₃ and then the aromatic reactant. In some cases the mixture is heated to 100 - 120° for some time, and sometimes excess of the acetyl chloride is used instead of a solvent. The efficiency of the acyl halides used decreases in the series I > Br > Cl > F, while the Friedel-Crafts catalysts have effects
decreasing in the order \( \text{SnCl}_4 > \text{FeCl}_3 > \text{ZnCl}_2 > \text{AlCl}_3 > \text{TiCl}_4 \). 

This general technique was applied to the acetylation of \( \gamma \)-phenyltetronic acid, using acetyl chloride. A variety of catalysts, solvents, temperatures and times of reaction was used and their effect determined by paper-chromatographic examination of the acidic product in each case using authentic \( \alpha \)-acetyl-\( \gamma \)-phenyltetronic acid as standard. 1.3 mol. equivalent of catalyst was sufficient to give maximum conversion. Where conversion to the \( \alpha \)-substituted compound had occurred to an extent greater than 40 - 50\% no colours were obtained with aqueous sodium nitrite.

The results obtained are tabulated. Total recovery is on a weight basis, but the conversion is that estimated by means of paper chromatograms.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Catalyst (1.3 mol. equiv.)</th>
<th>Conditions</th>
<th>Total Recovery</th>
<th>Estimated Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetyl chloride</td>
<td>AlCl₃</td>
<td>4 hr, reflux</td>
<td>75</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>&quot;</td>
<td>&quot;</td>
<td>75</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>ZnCl₂</td>
<td>&quot;</td>
<td>50</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>&quot;</td>
<td>7 hr, reflux</td>
<td>30</td>
<td>95</td>
</tr>
<tr>
<td>Nitrobenzene</td>
<td>&quot;</td>
<td>4 hr, /120°</td>
<td>75</td>
<td>40</td>
</tr>
</tbody>
</table>

Zinc chloride, and stannic chloride even more, gave trouble during the course of extractions of the crude products, inorganic material causing emulsion formation. Filtration
did succeed in removing this but some reduction in recovery was inevitable.

It seemed, then, that not only did the $\gamma$-phenyltetronic acid nucleus survive Friedel-Crafts conditions but some $\alpha$-acetylation was occurring. Stannic chloride gave best conversion although allowing poorest total recovery, especially if too long a period of reflux was used, and the use of a solvent other than acetyl chloride decreased the conversion. The best conditions were therefore about 4 hours' reflux without solvent using stannic chloride as catalyst.

The task of isolating the $\alpha$-acetyl-$\gamma$-phenyltetronic acid in a pure state still remained. It had already been found that even pure authentic $\alpha$-acetyl-$\gamma$-phenyltetronic acid would not form a bisulphite compound, and although the $\alpha$-acetyl compound did sublime more readily than $\gamma$-phenyltetronic acid itself the difference was not enough to give complete separation. Methylation with diazomethane of the crude product (90% $\alpha$-acetyl compound) in ether was carried out and the resultant crude mixture was separated on a column of alumina into a small and a large fraction eluted by benzene and chloroform respectively. Only the small fraction would crystallise however, and was identified with authentic $\gamma$-phenyltetronic acid methyl ether by melting-point and mixed melting-point.

The crude $\alpha$-acetyl-$\gamma$-phenyltetronic acid, however, did form a phenylhydrazone which was purified by transference
to an alumina column and elution with benzene. The second, major fraction was recrystallised from ethanol and gave m.p. 156 - 157° (Lacey, loc. cit. gives m.p. 157 - 158°). For analysis, the crude \( \alpha \)-acetyl-\( \gamma \)-phenyltetronic acid was sublimed and then crystallised six times from light petroleum, after which it was chromatographically and analytically pure and had the expected m.p. 101 - 104° (mixed m.p. with standard specimen, 100 - 102°). The yield by this method of isolation was only about 20%.

\( \gamma \)-Phenyltetronic acid had served its purpose in allowing the best conditions for direct Friedel-Crafts substitution to be determined, and so attention was turned to the other tetronic acids. Here again stannic chloride was found to give the best results, with refluxing in a small excess of acetyl chloride as solvent for 2 - 4 hours. The results showed that \( \gamma \)-phenyltetronic acid had in fact been an unfortunate choice for the preliminary investigations, as the two \( \gamma \gamma \)-disubstituted acids gave better yields of the \( \alpha \)-acetyl derivatives. No acetyl derivatives were obtained with \( \gamma \)-methyl- or \( \gamma \)-spirocyclohexyltetronic acid, although a small amount of a substance which was probably \( \alpha \)-acetyl-\( \gamma \)-methyltetronic acid was detected chromatographically in the crude recovery of \( \gamma \)-methyltetronic acid. Total recovery of intact \( \gamma \)-methyltetronic acid was poor, as destructive degradation was extensive.
The complete results are tabulated. The yields are based on the weights of pure product isolated, while the extent of conversion was again estimated chromatographically.

<table>
<thead>
<tr>
<th>Reactant Tetronic Acid</th>
<th>Estimated Conversion</th>
<th>Yield of Acetyl Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>γ-Phenyl-</td>
<td>90</td>
<td>20</td>
</tr>
<tr>
<td>γγ-Diphenyl-</td>
<td>100</td>
<td>56</td>
</tr>
<tr>
<td>γ-Methyl-</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>γγ-Dimethyl-</td>
<td>100</td>
<td>58</td>
</tr>
<tr>
<td>γ-Spirocyclohexyl-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

The products had the melting-points reported by Lacey (loc. cit.) and their identity was supported by mixed m.p. with specimens prepared by Fries re-arrangements.

No pure products were isolated from attempts to introduce other α-substituent groups into γ-phenyltetronic acid by direct Friedel-Crafts substitution. Heating with stannic chloride in benzoyl chloride was shown chromatographically to give about 20% conversion to a new compound but the isolation was complicated by the benzoic acid produced. Succinic anhydride and AlCl₃ in nitrobenzene as solvent gave about 30% conversion to a new product.

γ-Methyltetronic acid heated with succinic anhydride and AlCl₃ in nitrobenzene gave the chromatographically pure unchanged tetronic acid; but by heating a mixture of
γ-methyltetronic acid and stannic chloride in a small excess of β-methoxycarbonylpropionyl chloride (I) (prepared according to the method of Robinson and Robinson, J., 1925, 127, 180) at 100° for 2 hours, a crude recovery was obtained which was run on a paper chromatogram against a standard mixture of pure γ-methyltetronic acid (brown spot at \( R_f \) 0.69) and authentic carolinic acid (bright orange spot, \( R_f \) 0.60) using as solvent system propanol/ammonia (0.880)/water (50:25:25, v./v./v.). Spraying with aqueous ferric chloride revealed that 5-10% conversion to a substance which was probably carolinic acid (II) had been achieved.

\[
\begin{align*}
\text{I} & \quad \text{OH} \\
\text{Me} & \quad \text{O} \\
\text{O} & \quad \text{CO}_\text{Cl} \\
\text{Me} & \quad \text{O} \\
\text{O} & \quad \text{CO}_\text{Cl}
\end{align*}
\]

The same acid chloride, with \( \text{SnCl}_4 \) as catalyst, gave about 60-70% conversion of \( \gamma \gamma \)-diphenyl- and \( \gamma \gamma \)-dimethyltetronic acids to new compounds (nitrite tests on crude products negative) but no products were isolated.

Two attempts at Friedel-Crafts alkylation were made on \( \gamma \)-phenyltetronic acid, using ethyl bromide and stannic chloride, and benzyl chloride and aluminium chloride respectively. Only pure \( \gamma \)-phenyltetronic acid was recovered from both.
Fries Re-arrangement.

The Fries reaction of phenolic esters, usually carried out in presence of a Friedel-Crafts catalyst, results in the o- or p-hydroxy-ketone. It has recently been interpreted (Baltsby at al., J. Amer. Chem. Soc., 1955, 77, 2522) as proceeding through a complex of phenol ester and catalyst which becomes polarised according to the following scheme:

\[
\begin{array}{c}
\text{I} \\
\text{Ia.} \\
\text{I} \text{a.}
\end{array}
\]

It is obvious that as the polarisation of the conjugate acid increases, not only does the acyl portion become more electrophilic but also the phenolic portion acquires a higher electron density and is itself more subject to attack. When the complex is sufficiently polarised it becomes capable of acylating a different molecule or of re-arranging. The former process would follow the usual rules of orientation while the latter one would expect to afford only the p-hydroxy-ketone.

Depending on the susceptibility to electrophilic attack of various aromatic species present, various degrees of polarisation would suffice to produce rapid substitution. In
the Friedel-Crafts reaction itself a similar polarised, but not ionised, complex may be the reagent and since the Fries reaction proceeds more slowly than the Friedel-Crafts substitution reaction, one may expect that polarisation is less facile with \( \text{Cl}_3\text{Al} \cdot \text{O(Ph)CO}_2\text{R} \) (I) than with \( \text{Cl}_3\text{Al} \cdot \text{ClCOR} \).

By and large, it may be presumed that attack in the phenolic portion is readiest para to the oxygen and substitution by another molecule will take place there by preference. At the same time, the ortho positions to the oxygen will become somewhat sensitive, but the activation energy in these positions will tend to be greater than in the para position, and it is believed that little intermolecular \( \sigma \)-substitution occurs where the \( \pi \)-position is available.

Rosenmund and Schnurr (Ann., 1927, 460, 56) summarised the experimental findings in the general rule that high temperatures favour the \( \sigma \)-shift and low (using nitrobenzene as a solvent) the \( \pi \).

A true intramolecular \( \sigma \)-rearrangement, however, is favoured by steric factors and can be regarded as an intramolecular electrophilic substitution reaction or, in reverse, as a nucleophilic re-arrangement of the Whitmore type:

\[
\begin{align*}
\text{Cl}_3\text{Al} \cdot \text{O(Ph)CO}_2\text{R} & \quad \rightarrow \\
\text{Cl}_3\text{Al} \cdot \text{ClCOR} & 
\end{align*}
\]
Since in general this intramolecular re-arrangement requires a higher state of activation it is reasonable that it can predominate only at higher temperatures. Only when independent electronic influences within the phenolic portion of the system activate an o-position can o-rearrangement predominate even under mild conditions (e.g. Coulthard et al., J., 1930, 280; Baltsby and Bass, J. Amer. Chem. Soc., 1933, 55, 4292).

It appears, then, that the Fries reaction may be considered as a true Friedel-Crafts reaction or as an intramolecular change. The intermolecular process accounts for the re-arrangements found to occur in the positions normally substituted in aromatic compounds, while intramolecular changes can probably afford only o-hydroxy-ketones. The true intramolecular re-arrangement process, however, may not predominate in cases - for example with the esters of o-cresol - in which an intermolecular process would also give o-substitution.

The normal experimental technique is to dissolve the Friedel-Crafts catalyst, with stirring, in slightly more than the minimum amount of dry nitrobenzene, continue the stirring until heat of solution is dissipated and then add the ester. As in the Friedel-Crafts reactions, too large an excess of catalyst may give isomerisation.

The reaction mixture is stirred, allowed to stand or heated if necessary, and hydrolysed with cracked ice and HCl.
The preparation of the enol esters of tetronic acids, for use in Fries reactions, presented no difficulties. Like the esters of phenols, they are produced by the action of acid chlorides or anhydrides on tetronic acids or their alkali salts (Schotten-Baumann). Like the esters of phenols, too (and like the esters of aliphatic alcohols) they are decomposed into their components by heating with alkalis.

The enol acetates of $\gamma$-phenyl-, $\delta\delta$-diphenyl-, $\alpha$-methyl-, $\delta\delta$-dimethyl-, and $\gamma$-spirocyclohexyltetronic acids were prepared as follows.

The tetronic acid was ground with a small excess of the equivalent amount of acetic anhydride, some drops of conc. $\text{H}_2\text{SO}_4$ were added and the solution was allowed to stand at room temperature for some time. The neutral ester was purified by dilution with chloroform and washing with sodium bicarbonate solution, and crystallising the solute from light petroleum (yields 68 - 81%). Analytically pure specimens were obtained in most cases.

The enol benzoates of the same five acids were also prepared. The tetronic acid, in a solution of sodium carbonate, was shaken with an equivalent amount of benzoyl chloride and allowed to stand for a day. Solid material was collected by filtration, dried and crystallised to analytical purity from light petroleum. Yields varied from 62% to 82% of theoretical weights.

For determining the optimum conditions for rearrangement
the enol esters of γ-phenyltetronic acid were used. The enol acetate first, with nitrobenzene or carbon disulphide as solvent, was heated with different catalysts for different times and at different temperatures. Products were examined chromatographically, and the results tabulated. As usual, total recoveries and yields are on a weight basis, but conversions are based on chromatograms.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Total Recovery</th>
<th>Estimated Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>AlCl₃</td>
<td>Nitrobenzene</td>
<td>60⁰/0.25 hr. + 20⁰/18 hr.</td>
<td>90</td>
<td>-</td>
</tr>
<tr>
<td>1.3 m. equiv.</td>
<td>150⁰/0.25 hr. + 20⁰/18 hr.</td>
<td>70</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>CS₂</td>
<td>46⁰/3 hr. + 100⁰/0.5 hr.</td>
<td>90</td>
<td>-</td>
</tr>
<tr>
<td>SnCl₄</td>
<td>Nitrobenzene</td>
<td>100⁰/2.5 hr.</td>
<td>77</td>
<td>50</td>
</tr>
<tr>
<td>1.3 m. equiv.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZnCl₂</td>
<td></td>
<td>100⁰/2.5 hr.</td>
<td>91</td>
<td>75</td>
</tr>
<tr>
<td>1.3 m. equiv.</td>
<td></td>
<td>100⁰/4 hr.</td>
<td>50</td>
<td>90</td>
</tr>
</tbody>
</table>

These results indicated that ZnCl₂ and SnCl₄ were both superior to AlCl₃ for effecting conversion to the α-acetyl-γ-phenyltetronic acid, although both gave more trouble in removing inorganic material.

The product from the last experiment (90% conversion)
was separated on 10 paper chromatograms of 3 mm. paper. These were irrigated with the usual solvent, dried and photographed and then lightly sprayed with dil. HCl. The portions containing \( \alpha \)-acetyl-\( \gamma \)-phenyltetronic acid were removed and continuously eluted with ethanol. The solvent was removed and the residue was purified by crystallisation from light petroleum. The pure product had m.p. 104 - 106\(^\circ\); mixed m.p. with authentic specimen, 104 - 105\(^\circ\). The compound was chromatographically pure and gave no colour with aqueous sodium nitrite, indicating \( \alpha \)-substitution.

Attention was next directed to the enol acetates of the other four tetronic acids. Rearrangements were attempted in nitrobenzene as solvent using different catalysts and conditions.

<table>
<thead>
<tr>
<th>Enol Acetate of</th>
<th>Catalyst</th>
<th>Conditions</th>
<th>Estimated Conversion</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \delta \gamma )-diphenyltetronic acid</td>
<td>ZnCl(_2)</td>
<td>100(^\circ)/2 hr.</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&quot;</td>
<td>AlCl(_3)</td>
<td>100(^\circ)/5 hr.</td>
<td>90</td>
<td>-</td>
</tr>
<tr>
<td>&quot;</td>
<td>SnCl(_4)</td>
<td>&quot;</td>
<td>100</td>
<td>63</td>
</tr>
<tr>
<td>( \gamma )-methyltetronic acid</td>
<td>SnCl(_4)</td>
<td>100(^\circ)/3 hr.</td>
<td>50</td>
<td>-</td>
</tr>
<tr>
<td>( \delta \delta )-dimethyltetronic acid</td>
<td>SnCl(_4)</td>
<td>100(^\circ)/2 hr.</td>
<td>100</td>
<td>71</td>
</tr>
<tr>
<td>( \gamma )-spirocyclohexyltetronic acid</td>
<td>SnCl(_4)</td>
<td>100(^\circ)/2 hr.</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Stannic chloride, it seemed was the most widely applicable of the Friedel-Crafts catalysts.

Although \( \alpha \)-acetyl-\( \gamma \)-methyltetronic acid itself could not be isolated, the crude product reacted with phenylhydrazine in boiling benzene to give a phenylhydrazone m.p. 165°. (Lacey, loc. cit., gives m.p. 165°).

The re-arrangement of the tetronic acid enol benzoates was slightly less successful than that of the enol acetates. (Similar results are obtained to a less extent, in the phenolic series.) Stannic chloride, with nitrobenzene as solvent, was used. Two new compounds were isolated - \( \alpha \)-benzoyl-\( \gamma \gamma \)-dimethyltetronic acid, and \( \alpha \)-benzoyl-\( \gamma \)-spirocyclohexyltetronic acid. All except \( \gamma \)-methyltetronic acid did give some re-arrangement:

<table>
<thead>
<tr>
<th>Enol Benzoate of</th>
<th>Conditions</th>
<th>Estimated Conversion</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \gamma )-phenyltetronic acid</td>
<td>100°/4 hr.</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>( \gamma \gamma )-diphenyltetronic acid</td>
<td>&quot;</td>
<td>50</td>
<td>-</td>
</tr>
<tr>
<td>( \gamma )-methyltetronic acid</td>
<td>&quot;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>( \gamma \gamma )-dimethyltetronic acid</td>
<td>&quot;</td>
<td>100</td>
<td>77</td>
</tr>
<tr>
<td>( \gamma )-spirocyclohexyltetronic acid</td>
<td>&quot;</td>
<td>95</td>
<td>71</td>
</tr>
</tbody>
</table>
**Hoesch Reaction.**

The last of the typically phenolic reactions to be studied which might lead to $\alpha$-acetyl tetronic acids, was the Houben-Hoesch synthesis. Phenols, polyhydric phenols (especially those with hydroxyl groups meta to one another), and phenolic ethers readily react with aliphatic or aromatic nitriles in the presence of HCl to form ketiminochlorides, which on boiling with water yield the corresponding ketones, e.g. phloroglucinol gives phlorobenzophenone.

![Chemical structure of Hoesch Reaction](image)

When phenols are used, however, imino ether hydrochlorides are sometimes by-products or the only products.

The reaction may be regarded as an extension of Gattermann's aldehyde synthesis wherein a phenolic compound is treated with HCN and HCl, in some cases with the addition of condensing agents such as AlCl$_3$ or ZnCl$_2$. Iminoformic acid chloride (I) is first formed which then reacts with the phenol with elimination of HCl to give an aldoimine. The latter, on heating with dilute acids, is readily converted into the aldehyde itself.

![Chemical structure of Gattermann Reaction](image)

The Gattermann reaction can be applied to both phenols and aromatic ethers.
There are two views of the mechanism of the Hoesch reaction. Hoesch regarded the reaction as having three stages:

a) Formation of iminochloride, \( \text{RCN} + \text{HCl} \rightarrow \text{RCOC}_6\text{H}_4\text{Cl} \) (II)

b) Reaction with phenol to give ketimine hydrochloride

\[ \text{R}, \text{C}_6\text{H}_4\text{OH} \quad \text{NH}_{\text{HCl}} \]

c) Hydrolysis to ketone, \( \text{RCOC}_6\text{H}_4\text{OH} \)

Stephen, on the other hand (J., 1920, 117, 1529) postulated the reaction of the iminochloride (II) with the phenolic hydrogen to form an imino-ether which might then (1) rearrange to a ketimine hydrochloride ("normal" Hoesch reaction) or (2) if properly constituted condense internally to a coumarin or dihydrocoumarin ("abnormal" Hoesch reaction). This seems untenable, however, since such imino ether hydrochlorides cannot be rearranged; and in any case the reaction goes even when the phenolic OH is methylated.

The usual method is to dissolve equimolar quantities of the reactants in dry ether, preferably in presence of a catalyst, and to introduce dry hydrogen chloride during cooling to \( 0^\circ \). Several solvents have been used successfully in place of ether, such as glacial acetic acid, chloroform, methyl and ethyl acetates and ethyl bromide. Dioxane, acetic anhydride, dimethyl ether and benzene have been found to be unsuitable. Iminochlorides - the intermediates - have been used in place of the nitriles. The solid which appears is usually collected
and treated with water at room temperature, or with warming, until a precipitate appears of the product. If the ketimine hydrochloride is soluble in ether to some extent, the reaction mixture may be treated with water and the ether layer removed. The aqueous solution is heated and the ketone which separates is filtered or extracted with a solvent. Hydrolysis may be facilitated by dilute aqueous ammonia, sodium hydroxide, CaCO₃, dil. HCl, or dil. H₂SO₄; ethanol and aqueous ethanol have also been used but make isolation of pure ketone difficult. Isolation of the ketimine is better when no catalyst has been necessary.

Using this information, various attempts were made to prepare α-acetyl-γ-phenyltetronic acid by means of the Hoesch reaction. All were unsuccessful.

A solution of α-acetimido-γ-phenyltetronic acid in dry ether was saturated with hydrogen chloride and evaporated. The residue was merely unchanged α-acetimido compound, instead of the ketimine hydrochloride (III) which would be the intermediate in the Hoesch synthesis.
The normal Hoesch technique using a suspension of equimolar amounts of \( \gamma \)-phenyltetronic acid, zinc chloride and acetonitrile in dry ether and saturating with hydrogen chloride (dissolution resulting) gave only unchanged \( \gamma \)-phenyltetronic acid along with the iminochloride from acetonitrile, and a little neutral material which was probably \( \gamma \)-phenyltetronic acid enol acetate. A semi-crystalline oil which separated during the passage of hydrogen chloride contained only unchanged \( \gamma \)-phenyltetronic acid and the iminochloride, and the ether solution, washed with aqueous sodium bicarbonate, contained only the enol acetate. The bicarbonate washings contained only chromatographically-pure \( \gamma \)-phenyltetronic acid.

A solution of \( \gamma \)-phenyltetronic acid in ethyl acetate when saturated with hydrogen chloride was found to give a 61% yield of the ethyl ether. This was crystallised to analytical purity when it had m.p. 64° and showed \( \lambda_{\text{max}} : 2570 \ \text{R} \ (\log E 2.4) \). An attempt at a Hoesch reaction using dry ethyl acetate as solvent resulted only in the same ether, which was hydrolysed by 10% aqueous sodium hydroxide to chromatographically-pure \( \gamma \)-phenyltetronic acid.

\( \gamma \)-Phenyltetronic acid dissolved in nitrobenzene was treated with a slight excess of freshly prepared hydrochloride of acetonitrile and of zinc chloride and the mixture was heated at 120° for 0.5 hour and treated as in a Friedel-Crafts reaction. Only pure \( \gamma \)-phenyltetronic acid was recovered.
Grignard Reagents.

No reports are available on either the formation of reactive Grignard complexes by $\alpha$-halogeno-tetronic acids, or on the action of normal Grignard reagents on the tetronic acid nucleus.

The action of Grignard reagents on lactones was first investigated by Houben (Ber., 1904, 37, 489) who studied several of the reactions of coumarin (1, 2-benzopyrone) and similar lactones. These, he found, usually reacted to give 1, 2-benzopyran ($\Delta^3$-chromene) derivatives, e.g.:

\[
\begin{align*}
\text{O} & \quad \text{CH} & \quad \text{CH} \\
\text{C} & \quad \text{O} & \quad \text{C}
\end{align*}
\]

\[
\text{RMeX} \rightarrow \begin{align*}
\text{O} & \quad \text{CH} & \quad \text{CH} \\
\text{C} & \quad \text{O} & \quad \text{C}
\end{align*}
\]

The analogous closed-chain tetrahydrofuran derivative (II) (Kohn, Monatsh., 1913, 34, 1729) is obtained by allowing an ethereal solution of $\gamma$-$\delta$-dihydroxy-$\gamma$-$\delta$-dimethylvaleric acid $\gamma$-lactone (I) to react vigorously with 3 equivalents of phenylmagnesium bromide. But when the reaction is allowed to proceed in very high dilution the product is the open-chain tri-hydroxy compound (III) (Kohn and Osteretzer, Monatsh., 1916, 37, 37).

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{C} & \quad \text{C} \quad \text{O} & \quad \text{OH} & \quad \text{PhMgBr} & \rightarrow & \text{H}_2\text{C} & \quad \text{C} & \quad \text{C} \quad \text{O} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Ph} & \quad \text{Me} & \quad \text{Ph} & \quad \text{OH}
\end{align*}
\]

I II III
The open-chain glycol is the product obtained from many simple aliphatic \( \gamma \)-lactones, illustrating their internal ester structure:

\[
\begin{align*}
RHC \quad &\xrightarrow{H_2O} \quad RCH(OH)CH_2CH_2OH + 2MgXOH \\
RHO \quad &\xrightarrow{2R'MgX} \quad RCH(Omega)CH_2CH_2OMgX
\end{align*}
\]

Thus \( \gamma \)-butyrolactone with \( MeMgI \) gives \( HOCH_2CH_2CH_2(CH_3)_2OH \). Other \( \gamma \)-lactones reacting as esters are \( \gamma \)-valerolactone, \( \alpha \)-amino-\( \alpha \)-\( \gamma \)-dimethyl-\( \gamma \)-hydroxyvaleric acid \( \gamma \)-lactone and others.

The product which might arise from the tetronic acid nucleus (IV) with a Grignard reagent \( PhMgBr \) therefore seemed to be firstly the ring-opened glycol (V), by analogy with the simple aliphatic lactones, which could react further,

\[
\begin{align*}
IV \quad &\xrightarrow{R'R''} \quad R'R''(OH)COCH_2C(OH)Ph_2 \\
V \quad &\xrightarrow{Ph_2} \quad \text{Neutral Product}
\end{align*}
\]

Alternatively, the furan derivative (VI) was possible, which might also react further.

In fact, when \( \gamma \)-phenyl- and \( \delta \delta \)-diphenyltetronic acids were treated in ether with 2 and 3 moles phenylmagnesium bromide only chromatographically pure unchanged tetronic acid resulted, along with a small amount of a neutral product which was confirmed as being diphenyl (m.p. 71°) by mixed m.p., analysis, and U.V. light absorption.
Rearrangement of Allyl Ethers.

Originally the term "Claisen rearrangement" implied a thermal isomerisation in which an allyl group migrated from an oxygen atom to a neighbouring carbon atom, but there is a tendency to widen the scope of the term by including a number of reactions of formally similar nature which may or may not take place by a similar mechanism.

Allyl ethers of enols pass into the C-allyl ketone on heating, but the rearrangement is normally associated with allyl and substituted allyl ethers of phenols, which give nuclear allyl phenols. It seems that the essential group is C=C=O-CH2CH=CH2 where the C=C=O may be open-chain or aromatic. Allyl hydrogens may be substituted but the double bond cannot be changed in position or to a triple bond.

If a position ortho to the ether group is available it is almost always taken by the allyl group, and the use of an isotopically labelled group (Ryan and O'Connor, *J. Amer. Chem. Soc.*, 1952, 74, 5866; Schmid and Schmid, *Helv. Chim. Acta*, 1952, 35, 1879; Curtin and Johnson, *J. Amer. Chem. Soc.*, 1954, 76, 2276) has established that such α-rearrangement is accompanied by allylic inversion as in
Hence the concerted cyclic mechanism (I $\rightarrow$ III) for the ortho Claisen re-arrangement, first put forward by Claisen (Ber., 1925, 58B, 275) is acceptable, and can also be reconciled with data pertaining to reaction order, intramolecularity, activation energies and entropies. The mechanism can also be made to account for the curious retention of optical activity when optically active phenyl $\alpha$:$\gamma$ dimethyl allyl ether is heated at 200° (Alexander and Kluiber, J. Amer. Chem. Soc., 1951, 73, 4304).

The mechanism of the para Claisen rearrangement is different. It occurs as a rule only where no $\alpha$-position is vacant, although it also takes place with the mono-allyl ethers of some $\alpha$-dihydric phenols, even if the second phenolic hydroxyl group is alkylated. Steric considerations rule out the possibility of a cyclic mechanism between the $\alpha$-positions, and the retention of optical activity is only slight in the $\alpha$-rearrangement of 2:6 dimethylphenyl-$\alpha$:$\gamma$-dimethylallyl ether. Until recently a $\pi$-bond complex was regarded as the intermediate, S.E.?
but certain anomalous migrations have shown that this explanation is inadequate.

A logical extension of Claisen's cyclic mechanism for $\pi$-rearrangement suggests that a dienone of type II is the intermediate also in the $\pi$-migration, and Curtin and Johnson (loc. cit.) have obtained evidence for its reversible formation. A 2,2,6-trisubstituted cyclohexadienone has in fact been isolated as its maleic anhydride adduct (Conroy and Firestone, J. Amer. Chem. Soc., 1956, 78, 2290). The mechanism should therefore be represented by IV - VII:

\[
\begin{align*}
\text{IV} & \quad \text{V} & \quad \text{VI} & \quad \text{VII} \\
\begin{array}{c}
\text{O} \\
\text{R} \\
\text{CH}_2\text{CH}=\text{CH}_2
\end{array} & \rightarrow & \begin{array}{c}
\text{R} \\
\text{CH}_2\text{CH}=\text{CH}_2
\end{array} & \rightarrow & \begin{array}{c}
\text{H} \\
\text{CH}_2\text{CH}=\text{CH}_2
\end{array} & \rightarrow & \begin{array}{c}
\text{OH} \\
\text{CH}_2\text{CH}=\text{CH}_2
\end{array}
\end{align*}
\]

The second stage is analogous to the reversible first stage in being a thermal re-arrangement of a system in which both an allyl and a vinyl residue are attached to the same atom, although the central atom is $\mathrm{C}$ rather than $\mathrm{O}$. The last step is a return to an aromatic system. An important corollary of the dienone mechanism is of course that an allyl residue attached to the ether oxygen can gain equivalence with, exchange with, or displace one initially in the $\pi$-position.

Such a mechanism explains most of the anomalies involved in acceptance of the $\pi$-complex, such as the absence of allylic
inversion in \( n \)-migrations, and is in accord with the fact that \( n \)-migrations closely resemble the ortho in reaction conditions, energies and entropies of activation (Tarbell and Kincaid, J. Amer. Chem. Soc., 1939, 61, 3085). Both rearrangements, being intramolecular (Schmid and Schmid, Helv. Chim. Acta, 1953, 36, 489) and of first order (Tarbell and Kincaid, J. Amer. Chem. Soc., 1940, 62, 728; Alexander and Kluiber, loc. cit.) should have a common or similar rate-determining step, and the high negative entropy values suggest that this step involves a cyclic transition state.

Decarboxylation of \( \alpha \)- and \( \beta \)-carboxyphenyl allyl ethers has been observed frequently during both \( \alpha \)- and \( \beta \)-Claisen rearrangements (Claisen and Kieli, Ann., 1913, 401, 21; Tarbell and Wilson, J. Amer. Chem. Soc., 1942, 64, 607 and 1066; Nummy and Tarbell, J. Amer. Chem. Soc., 1951, 73, 1500; Curtin and Johnson, loc. cit.), and Conroy and Firestone (loc. cit.) point out that this is predictable from the diene mechanism, since the diones involved must be either \( \beta \)-keto acids or vinylogous \( \beta \)-keto acids.

The Claisen rearrangement is usually brought about by heat alone \( (100 - 250^\circ) \) without either solvent or catalyst. However, in some cases the use of dimethylaniline or diethylaniline has been recommended as solvent, and in other cases (e.g., Lauer and Kilburn, J. Amer. Chem. Soc., 1937, 59, 2586) it is claimed that the reaction is facilitated by the presence of ammonium chloride, e.g., the ether of acetoacetic ester. Side-reactions can be diminished by heating
in vacuo or in a non-oxidising atmosphere. The usual method of working-up is to remove the basic solvent if present with dilute mineral acid, dissolve the residue in a solvent and extract into alkali the phenolic product to separate it from neutral by-products and starting material.

The preparation of allyl ethers of the tetronic acids was accomplished by the Williamson method using allyl halides with a solution of the tetronic acid in sodium ethoxide. This method is regarded as particularly suitable for weakly acidic phenols (e.g., Bartz et al., J. Amer. Chem. Soc., 1935, 57, 371), although substituted allyl halides give some C-alkylation. A greater proportion of C-alkylation is observed with more active halides. The neutral allyl ethers were separated from the unchanged tetronic acids by pouring into water and extracting into ether. Drying and evaporating the extracts gave the ethers which, when purified by crystallisation or distillation, were crystalline solids. The allyl ether of \( \gamma \)-phenyltetronic acid was hydrolysed to the free tetronic acid by heating with 10% aqueous sodium hydroxide and was also readily reduced to the \( \beta \)-propyl ether in presence of 5% Pd/BaSO\(_4\) or the more severe Adams' catalyst. The same \( \beta \)-propyl ether was obtained by Williamson's method.

The method of rearrangement applied to the allyl ethers was to heat portions of 1 - 2 g, with an equal weight of ammonium chloride (approx. 3 molar equivalents) for periods of 18 hours at 100 - 120\(^\circ\)/0.01 mm, in a "cold finger" sublimation apparatus. The crude product resulting was
triturated with aqueous sodium bicarbonate and chloroform, so that acidic material was separated from neutral material. Acidification of the aqueous bicarbonate layer and extraction into ether finally yielded oils which were examined chromatographically. The allyl ether of \( \gamma \)-phenyltetronic acid was found to give about 20\% conversion to a new substance; that of \( \delta \delta \)-diphenyltetronic acid gave about 50\% conversion; while that of \( \delta \delta \)-dimethyltetronic acid gave a crude acidic product which gave no colour with sodium nitrite and appeared to consist of about 95\% of a new product and 5\% of \( \delta \delta \)-dimethyltetronic acid. The crude rearrangement product sublimed at \( 150^\circ/0.01 \text{ mm.} \) to a crystalline solid which was recrystallised from light petroleum to give what was probably the pure \( \alpha \)-allyl-\( \delta \delta \)-dimethyltetronic acid. The ammonium chloride seemed to be necessary, since distillation of the \( \gamma \)-phenyltetronic acid allyl ether at reduced pressure and high temperature resulted only in a neutral distillate, although this did not crystallise readily. The recrystallised sublimate had \( \lambda_{\text{max.}} \) \( 2550 \text{ \AA} \), \( \log \varepsilon 4.85 \) - the typical spectrum for a tetronic acid unmodified by conjugation.

**Attempted C-Alkylation.**

Apart from the work described in section II, only one attempt at C-alkylation of an \( \alpha \)-unsubstituted tetronic acid has been reported. J. R. Plimmer (op. cit., 115) attempted without success to introduce a \( \beta \)-butyl group into \( \gamma \)-phenyltetronic acid by means of syrupy phosphoric acid.
In the present work a method of C-alkylation used by Stetter and Dierichs (Ber., 1952, 85, 61) with β-diketones was applied to γ-phenyltetronic acid in order to obtain the model compound α-allyl-γ-phenyltetronic acid which should have resulted from a Claisen rearrangement. The method is applicable to compounds of the dimerone type, the best conditions involving a high concentration of potassium hydroxide in methanol with alkyl halide, sometimes with copper bronze and warming.

γ-Phenyltetronic acid was dissolved in 20% aqueous potassium hydroxide and stirred for 3 hours with allyl bromide and a little copper powder. After standing overnight the mixture was diluted with sodium hydroxide, filtered and washed with ether. The aqueous layer was acidified cautiously to pH 4 when a yellow oil and crystalline solid were precipitated. These were collected, dried and crystallised from light petroleum to give an 18% yield of a colourless solid m.p. 143 - 145°. Unchanged γ-phenyltetronic acid was recovered by further acidification of the aqueous solution to pH 2.

The first product gave a negative nitrite test, indicating α-substitution, and was chromatographically distinct from γ-phenyltetronic acid. Its U.V. absorption spectra showed ν max, 2500, log ε max, 4.15 typical of a β-keto enolisable tetronic acid derivative. Found: C, 62.04; H, 4.48 and C, 61.35; H, 4.72%. Active hydrogen content: 1.01%.
\[ C_{15}H_{12}O_3 \text{ requires } C, 72.21; \text{ H}, 5.59\%. \]  
\[ \alpha\text{-Hydroxy-\(\gamma\)}\text{-phenyltetronic acid requires: } C, 62.50; \text{ H}, 4.2; \text{ active H}, 1.04\%. \]

Attempts to acetylate the compound were unsuccessful, and tests with \(KMnO_4\) and iodine showed that although the substance had the reducing properties expected of an \(\alpha\)-diol system, \(\gamma\)-phenyltetronic acid itself had almost similar properties. However, the substance differed from \(\gamma\)-phenyltetronic acid in giving a strong purple colour with \(2\)-dinitrobenzene in saturated aqueous solution with a few drops of alkali. This test is indicative of an \(\alpha\)-diol system (Fearon and Kawerau, Biochem. J., 1943, 37, 326) so that the compound must be formulated as \(\alpha\text{-hydroxy-\(\gamma\)}\text{-phenyltetronic acid}, an analogue of ascorbic acid.

It is not clear how the substance arose, since an experiment using the allyl enol ether in place of the tetronic acid, and another omitting the allyl bromide, gave no reaction. Nevertheless, the I.R. spectrum of the compound can be reconciled with the proposed structure.
DISCUSSION.

The practical importance of these results need not be emphasized. New routes are provided to the $\alpha$-acyltetronic acids, including the new $\alpha$-benzoyltetronic acids, and a substance which is probably the first $\alpha$-allyltetronic acid has been obtained. More investigation is required, however, to find the requisite conditions for increasing the scope and yields of the reactions.

The theoretical implication of the work does merit some discussion, as it emphasises the fact that the tetronic acids cannot be classed merely as aliphatic compounds, although they are the cyclic analogues of $\beta$-keto-esters and can be compared to them and to $\beta$-diketones in several respects. The reactions of acetoacetic ester are characteristic of the ester of either a keto-acid or an unsaturated hydroxycrotonic acid. With hydrazine and its monosubstitution products acetoacetic ester yields normal phenylhydrazone. Hydroxylamine similarly condenses to give the oxime, $\beta$-isonitrosobutyric ester which readily cyclises to give methyl isoxazolone (I). Sodium bisulphite and HCN also react with acetoacetic ester in its ketonic form. All except the last two reactions are duplicated in the tetronic acid series.

\[
\begin{align*}
\text{CH}_2 & \quad \text{C}_2\text{CH}_3 \\
\text{CO} & \quad \text{N} \\
0 & \quad 0 \\
\end{align*}
\]

I
The structures differ to some extent in the reactions of the respective \( \alpha \)-methylene groups. Both react with nitrous acid, the tetronic acids to give \( \alpha \)-oximido-tetronic acids, ethyl acetoacetate to give ethyl isonitroso-acetoacetate. C-alkylation takes place more easily in the acyclic compounds than in tetronic acids. Stetter and Dierichs (Ber., 1952, 85, 61) found that \( \beta \)-diketones can be readily alkylated by using a high concentration of the potassium salt in methanol with alkyl iodide, while Stork (J. Amer. Chem. Soc., 1954, 76, 2029) has described a new synthesis of 2-alkyl- and 2-acyl-ketones involving the reaction of the condensation products of ketones with secondary amines and halogenc-compounds as electron acceptors.

The modification of the \( \alpha \)-methylene group in the tetronic acids, and the general stability to alkali of the tetronic acid nucleus is generally attributed to resonance. The anion produced in alkaline solution has considerable resonance possibilities which stabilise it against further attack (II). This explanation is, however, inadequate since both ethyl acetoacetate and \( \alpha \)-ethoxycarbonyltetronic acids undergo "ketonic hydrolysis" while possessing similar resonance possibilities and structure to those of the tetronic acids. A similar \( \beta \)-keto acid structure in the dienone intermediate is said to be responsible for the decarboxylation of \( \alpha \)- and \( \beta \)-carboxyphenyl allyl ethers during Claisen rearrangements (Conroy and Firestone, loc. cit.). It seems probable that the cyclic structure is at least partly responsible for the
Acidity.

A further difference from the acyclic analogues emphasises the anomalous nature of tetronic acids. The tetronic acids in general, and in particular the \(\alpha\)-halogenotetronic acids, are considerably stronger acids than the corresponding acyclic analogues. The acidity of a \(\beta\)-keto acid ester, however, depends on the constitution in a manner to be found purely by experiment. Arndt (Ann., 1932, 492, 258) has given an account of the difficulties involved, and as yet no satisfactory theory has been developed to correlate the facts.

For example, methyl acetoacetate is not acidic enough to be able to react with diazomethane, its salts are split hydrolytically by water, and the ester therefore does not dissolve in aqueous ammonia or dilute alkali. Ethyl acetoacetate, on the other hand, demonstrates its possession of a hydroxyl group by reacting with diazomethane to give an enol ether, and by dissolving in dilute alkali and aqueous ammonia. Again, the salts of ethyl acetoacetate are decomposed by \(\text{CO}_2\), whereas cyclopentanone carboxylic ester is such a strong acid that its salts are stable to \(\text{CO}_2\).
The dissociation constants of tetronic acid and several related compounds have been measured by W. D. Kumler (J. Amer. Chem. Soc., 1938, 60, 859). He was able to show by analysis of the salts of tetronic acid (I) that the enolic hydroxyl was responsible for its acidity, and the high measured value of the dipole moment (4.72D in dioxan) he reconciled with a calculated figure by proposing a resonance contributing form (II) involving charge-separation and fixation of the H atom of the enolic group over the α-carbon atom.

![Diagram](image)

- **I**
- **II**

<table>
<thead>
<tr>
<th></th>
<th>pKₐ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Chlorotetronic acid</td>
<td>2.13 ± 0.013</td>
</tr>
<tr>
<td>α-Bromotetronic acid</td>
<td>2.23 ± 0.005</td>
</tr>
<tr>
<td>α-Iodotetronic acid</td>
<td>2.31 ± 0.005</td>
</tr>
<tr>
<td>Tetronic acid</td>
<td>3.76 ± 0.003</td>
</tr>
<tr>
<td>α-Hydroxytetronic acid</td>
<td>4.37 ± 0.02</td>
</tr>
<tr>
<td>Ethyl α-iodoacetacetate</td>
<td>7.0</td>
</tr>
<tr>
<td>Ethyl acetacetate</td>
<td>10.7</td>
</tr>
</tbody>
</table>

Kumler (J. Amer. Chem. Soc., 1940, 62, 3292) points out that the acidic strengths of the tetronic acids should be very close to those of β-diketones (tetronic acid Kₐ 1.7 x 10⁻⁴, acetyl acetone Kₐ 1.3 x 10⁻⁵) and not to those of the β-ketonic
esters. The $\beta$-ketonic esters are weaker acids than the $\beta$-diketones, which possess only two contributing forms (III and IV) for both undissociated and dissociated molecules, because although the former have a third resonance form (VII) it stabilises the undissociated acid relative to the ionic form owing to an unfavourable charge distribution in the latter. The corresponding form (X) probably cannot participate in the tetronic acid resonance as it would necessitate two double bonds in the ring; but contribution by form (X) would in fact give greater acid strength. It should be noted that in acetoacetic ester the absence of conjugation in the forms XI and XII precludes their participating in the resonance owing to energy considerations. The contribution of form IX is mentioned in the section on ethers, and does seem to be appreciable.

The fact that tetronic acids have stronger acidity than $\beta$-diketones must be due either to the third resonance form (X) or to the cyclic structure. Inclusion of a $\beta$-diketonic system in a cyclic system prevents the hydrogen bonding which tends to diminish acidity in compounds such as acetyl acetone (Fawcett, Chem. Rev., 1950, 47, 250).

The degree of ring-strain is probably important, since the five-membered tetronic acid is a stronger acid ($pK_a 3.76$) than a six-membered analogue ($pK_a 5.15$) prepared by Brown, Henbest and Jones (J., 1950, 3634) although this substance is also very stable and largely enolised, and cannot be induced to ring-open with alkali.
**β-Diketones.**

Enol, \( R_2 C = CH \cdot CO \cdot R \)

Ion, \( R_2 C = CH \cdot CO \cdot R \)

**β-Ketonic esters.**

Enol, \( R_2 C \cdot (OH) = CH \cdot COOR \)

Ion, \( R_2 C \cdot (OH) \cdot COOR \)

**Tetronic acids.**

Enol, \( \text{[diagram of tetronic acid enol form]} \)

Ion, \( \text{[diagram of tetronic acid ion form]} \)
It is, at any rate, remarkable that tetronic acid is not only a stronger acid than its acyclic analogue but a stronger acid than acetic acid, whose vinylogue it is.

**Enolic-Ketonic Tautomerism.**

In enol-keto tautomeric systems no relationship has been recognised between the acidity and the position of the equilibrium between the keto- and the enol- forms. Thus for example the strongly acidic cyclopentanone carboxylic acid ester contains only 4% enol (depicted in I as its chelate form) while the weakly acidic cyclohexanone carboxylic acid ester contains 76% enol (Dieckmann, *Ber.*, 1922, 55, 2470; Russell, *Chem. and Ind.*, 1956, 326). Ethyl acetoacetate, with approximately the same weak acidity, contains only 7% enol

![Diagram](image)

but the strongly acidic tetronic acids (Kumler, *J. Amer. Chem. Soc.*, 1938, 60, 859; Jones and Whiting, *J.*, 1949, 1419) are now accepted as existing 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 the ketonic form. That the enolic hydroxyl can arise only from the active methylene group in the acetoacetatic ester and in tetronic acids is shown by the fact that dialkylation in that position deprives the ester or acid of any acidic properties whatever.
The presence of enol in a tautomeric mixture is indicated by the production of a colour with ferric chloride solution; anomalous results from this test can be explained by steric effects (Morgan and Drew, J., 1924, 125, 746). The only acidic tetronic acid which does not give an immediate colouration with FeCl₃ is γδ-dimethylditetronic acid.

**Substitution Reactions.**

The resonance in the tetronic acid nucleus not only affects the stability and physical properties of the system, such as light absorption, but permits substitution reactions to occur many of which are commonly accepted as diagnostic of aromaticity. G. N. Badger ("Structures and Reactions of Aromatic Compounds", Cambridge University Press, 1954, 2) summarises the properties of aromatic compounds and the extent to which the tetronic acids measure up to this standard is remarkable.

"(1) The most characteristic property of the aromatic compounds is their stability and ease of formation by pyrolytic methods."

------- The oldest established method of preparing tetronic acids is by heating α-substituted β-keto esters.

"(2) (Although saturated hydrocarbons are not usually attacked in the liquid phase by reagents such as HNO₃, H₂SO₄ and Br₂ and although olefins usually react by addition, the aromatic compounds tend to react by substitution with greater or less facility."

------- α-Nitrotetronic acid is prepared by nitration of tetronic
acid at -5°; α-iodotetronic acid is obtained by the action of iodine on a cold solution of tetronic acid; tetronic acid α-sulphonic acid is prepared by the action of fuming sulphuric acid on tetronic acid (Wolff and Luttringhaus, Ann., 1900, 312, 119); α-bromotetronic acid is prepared by bromination of tetronic acid in chloroform (Wolff and Schwabe, Ann., 1896, 221, 266).

"(3)(a) The aromatic amines are less basic than the aliphatic amines and react with nitrous acid to give diazo-compounds."

Aminotetronic acids are obtainable by the methods normal for aromatic amines and can be diazotised (Lecocq, Bull. Soc. chim. 1954, 18, 183; cf. Michael and Mittag, Z. physiol. Chem. 1937, 247, 34) like the α-aminophenols to give diazo-oxides. These have the structure I since they do not have the normal properties of diazo-compounds (Wolff, Ann., 1900, 312, 119). Again like the aminophenols,

![I]

aminotetronic acids are very easily oxidised.

"(b) The phenols are more strongly acidic than the aliphatic hydroxy-compounds (alcohols). The aromatic acids are somewhat stronger acids than the corresponding aliphatic acids."

Both tetronic acid itself and α-hydroxytetronic acid
are stronger acids than phenol. α-Carboxytetronic acids are too unstable to isolate.

"(a) The aromatic halogen compounds are much less reactive than the aliphatic halogen compounds (provided the former are not activated by suitable groups)."

The use of sodium amalgam or catalytic reduction (Clutterbuck, Raistick and Reuter, Biochem. J., 1935, 29, 1300) replaces the bromine in α-bromotetronic acid with hydrogen, but the bromine atom is relatively unreactive towards attack by aqueous alkali or ethanolic potassium acetate. Michael and Jung (Ber., 1933, 66B, 1291) succeeded in replacing the halogen in α-bromotetronic acid but the resulting α-hydroxytetronic acid was not obtained pure.

"(4) Parent aromatic substances are, in general, remarkably stable to oxidising agents."

The tetronic acid nucleus is comparatively resistant both to reduction and to oxidation. Both α-ketonic groups and allyl ethers can be reduced catalytically without affecting the tetronic acid nucleus, even if the relatively powerful Adams catalyst is used. No information is available on the ease of oxidation of tetronic acid ethers where the αβ-double bond is fixed, except that α-hydroxytetronic acid oxidises readily owing to its ene-diol system, as do the dihydric phenols in alkaline solution.

The successful application of the Friedel-Crafts, Fries and Claisen reactions so adds to the comparison between
aromatic phenols and tetronic acids that it seems justifiable to class them with the phenols instead of with the $\beta$-keto esters as their cyclic analogues.

Methods of $\alpha$-acylation other than Friedel-Crafts are reported with aromatic compounds and might be tried with tetronic acids. Acetylation can be carried out using solutions of perchloric acid in acetic acid and acetic anhydride (Hydon, *Ann. Rep.*, 1950, 156) or by acetyl perchlorate (Burton and Praill, *J.*, 1950, 1203 and 2034). Polyphosphoric acid as a condensing agent has very wide applicability (Snyder and Elston, *J. Amer. Chem. Soc.*, 1955, 77, 364). Another catalyst with wide application in electrophilic aromatic substitutions involving halogeno-compounds has recently been reported in silver tetrafluoroborate (Olah et al., *Chem. and Ind.*, 1957, Jan. 12th, 50).

The substitution in the tetronic acid nucleus may be regarded as substitution of an aromatic type or of an unsaturated compound. The modern conception of the mechanism of halogenation is complex. Substitution and addition seem to proceed side by side concurrently to give an intermediate product by a primary addition process. This however is something different from the stable, valence-chemically saturated substance which used to be the classical conception of the intermediate product.

The mechanisms of sulphonation and nitration of aromatic and unsaturated compounds are more understandable. The appearance of the $-\text{NO}_2$ group in unsaturated hydrocarbons is due not to $\text{HO-NO}_2$ fission and addition but to reduction of $\text{HNO}_3$. 
to oxides of nitrogen which add on to the double bond (Michael and Carlson, *J. Org. Chem.*, 1940, 5, 1 and 14). Elimination of H₂O then follows. Similarly, H₂SO₄ never adds on to an unsaturated compound by the fission HO·SO₂H, but adds on as pyrosulphuric acid (SO₂H)₂O (Michael, *J. Amer. Chem. Soc.*, 1936, 58, 294).

In aromatic compounds all evidence demands a different mechanism from the addition followed by elimination of H₂O. In electrophilic attack there is no definite evidence that any intermediate compound capable of existence as an individual is ever found; i.e., the reaction appears to be of the S₂2 type and can be formulated as

\[ \text{X} \rightarrow \text{Ar} \rightarrow \text{H} \]

where the attacking ion adds on to the C atom of the benzene ring and the H on the same carbon leaves as a proton.

The tetronic acid nucleus one would expect to react by direct aromatic substitution rather than by addition to the unsaturation centre followed by elimination of water. The double bond is resistant, for example, to the addition of hydrogen and the intermediate of an addition mechanism would be a saturated lactone and unstable in acid. It is perhaps significant, however, that recoveries in these reactions are poor.

In the Friedel-Crafts reaction unsaturated compounds differ from aromatic compounds in that they react only with acyl halides, and not with alkyl halides. Tetronic acids do not react with alkyl halides and are recovered unchanged, although the reason that unsaturated compounds fail to react
is generally accepted as being that AlCl₃ destroys these substances more quickly than they can undergo reaction with the less reactive organic alkyl halides.

When the unsaturated hydrocarbons such as cyclohexene are reacted with acyl chlorides the normal product results along with some β-chloroketone so that possible reaction paths are:

Because of the reversibility of III the β-chloroketone may arise just as well by the roundabout path I + III as by the direct path II (Huckel, "Theoretical Principles of Organic Chemistry", I., Elsevier Publishing Co., N.Y. 1955, p. 759).

This formulation of the possible reaction paths is exactly the same as in the aromatic compounds. According to Huckel:

"There is not the slightest reason or evidence that the chemical mechanism involved is a different one, as is the case in nitration and sulphonation. But as to which of the paths I or II + III is the correct one no answer is as yet forthcoming."
Electronic Structure.

It seems, then, that there is no obvious fundamental difference in the mechanisms of acylation in the aromatic and unsaturated compounds. Moreover, rearrangements of the Fries and Claisen type are quite common outside the aromatic series. For example, ethyl 0-allylacetoacetate rearranges in 85% yield when heated at 150 - 200° with NH₄Cl (Tarbell, Org. Reactions, II, 1941), while heterocyclic enolic allyl ethers rearrange without catalysts on heating for a short time at 200° (Jones and Trikojus, J. Amer. Chem. Soc., 1932, 54, 2570). Allyl kojate (I) when heated in nitrogen at 180 - 200°/0.1 mm. gives 6-allylkojic acid (McLamore et al., J. Amer. Chem. Soc., 1956, 78, 2816).

4'-Acetoxycoumarin rearranges with pyridine and piperidine to give in 60% yield 3-acetyl-4'-hydroxycoumarin (Eisenhauer and Link, J. Amer. Chem. Soc., 1953, 75, 2044).

\[
\begin{align*}
\text{CH}_2=\text{CH}.\text{CH}_2O & \\
\text{CH}=\text{CH} & \\
\text{CH}_2\text{OH}
\end{align*}
\]

Since it is reactions such as these which are normally accepted as diagnostic of aromaticity, it is a little surprising that the classical theory still maintains that "aromatic character requires the presence of six electrons which could normally not be placed in the ring or could be placed therein only in 3-electron bonds" (Hückel, op. cit., 674). This is comparable to the original requirement stated by Bamberger (Ann., 1890,
of six "potential" valences for the creation of the aromatic state, and includes heterocyclic compounds by virtue of the free "lone pairs" of electrons on the heteroatoms. Wave-mechanical theory depicts this aromatic sextet as occupying a continuous cyclic molecular orbital, and leads to the definition of an aromatic compound as "a cyclic compound with a large resonance energy where all the annular atoms can take part in a single conjugated system" (Dewar, "The Electronic Theory of Organic Chemistry", Oxford University Press, 1949, 160; Badger, op. cit., 43).

These definitions were originally proposed since it is true that the benzenoid compounds, which have the most pronounced aromatic character, possess sextets and continuous cyclic molecular orbitals. But they imply a fundamental qualitative difference between compounds with those attributes and those which do not possess them, which does not seem to be justifiable experimentally. The true situation seems to be that there is a gradual quantitative change in aromatic character from the acyclic unsaturated compounds through dimerone, cyclopentadionone, tetronic acids and the heterocyclic compounds which reaches its maximum in the benzenoid compounds, from which the tetronic acids seem to differ markedly only in stability to heat. Reaction routes acceptable to the modern theories of substitution and rearrangement outlined in the Introduction can be depicted without involving such a cyclic orbital as these definitions require. Dewar, however, does suggest that the \( \pi \)-electrons are necessary, for an
attacking electrophilic particle attaches itself to the nucleus as a whole by means of them and is then free to move over the ring. It then seeks out the position of highest electron availability, expels the hydrogen atom at this point as a proton, and attaches itself to the C atom by an ordinary covalency.

Since the tetronic acids possess aromatic characteristics not found in the acyclic analogues these properties must be due in some measure to the cyclic structure. The lactone ring seems greatly modified, for the carbonyl group does not react with Grignard reagents, and possesses enough enolic character to react with diazomethane. The greatest electron density is, however, at the \( \beta \)-hydroxyl since the Fries rearrangements are normal and the AlCl\(_3\) must have added as usual to the O of the ester group.

A cyclic molecular orbital of the kind depicted by Dewar cannot be responsible for no resonance form of tetronic acid can be depicted in which all the annular atoms take part in a single conjugated system. A steric effect may be responsible, for the presence of a double bond in or near a 5-membered ring affects its stability in unexpected ways (Brown et al., *J. Amer. Chem. Soc.*, 1954, **76**, 467). The alternative is that a molecular orbital incomplete in the accepted way must be admitted to give aromatic character. In other words an even more general definition of aromaticity is required than that of Wilson Baker (*J.*, 1945, **258**) which
merely required a cyclic unsaturated compound containing at least two conjugated double bonds in the ring, interacting to some extent.

It should be noted that the resonance form X. (see p. 1054) might fulfill the requirements of Wilson Baker's definition. Kumler (loc. cit.) dismissed this form but Wheland ("Resonance in Organic Chemistry", John Wiley and Sons, Inc., N.Y. 1955, 86) suggests that just such structures are probably most responsible for the greater stability of furan over its C-analogue cyclopentadione where comparable structures are impossible.
EXPERIMENTAL DETAILS.

TWO SYNTHESSES OF α-ACETYL-β-PHENYLSTETRONIC ACID (with Mr. J. S. Slater.)

Method A:

\[ \text{C}_6\text{H}_5\text{CH(OAc)}\cdot\text{COCl} + \text{CH}_3\text{CO} \cdot \text{CHNa} \cdot \text{COOr} \rightarrow \text{C}_6\text{H}_5\text{CH(OAc)} \cdot \text{CO} \cdot \text{CH}_3 \cdot \text{COOr} \]

(i) Acetylmandelyl chloride (I)

This was prepared according to the method already described (loc. cit.), on a scale of 0.7 mol. The product distilled at 140 - 145°/20 mm. Yield 106.5 g. (72%).

(ii) Ethyl α-(acetylmandelyl)-acetoacetate (II)

Ethyl acetoacetate (13.0 g., 0.1 mol.) was added dropwise with stirring to sodium (2.3 g., 0.1 g. atom) in dry ether (100 ml.). The reaction was allowed to proceed overnight.

A solution of acetylmandelyl chloride (21.25 g., 0.1 mol.) in dry ether (50 ml.) was added dropwise to the mixture during continuous stirring and cooling in ice. The mixture was stirred for 3 hours at room temperature and shaken with crushed ice (100 g.). The aqueous layer was separated and extracted twice with dry ether (25 ml. portions). The combined ether extracts were washed twice with water, once with NaHCO₃ solution and then twice again with water. Ether was removed from the dried (Na₂SO₄) ether solution, leaving a neutral viscous yellow oil which did not crystallise. Yield of crude product 40.0 g.
(theoretical 30.6 g.).

(iii) Cyclisation to α-acetyl-γ-phenyltetronic acid (III).

The crude condensation product above (6 g.) was dissolved in the minimum amount of ethanol and NaOH solution (2 molecular proportions of 0.5 N) was added. More ethanol was added until a solution (150 ml.) was obtained. After standing at room temperature for 24 hours, the solution was acidified with dilute sulphuric acid. Pale yellow crystals were precipitated. These were collected, washed with a little water, dried and recrystallised from light petroleum (b. 60 - 80°). M.p. 102 - 104° (Lecocq, Compt. rend., 1946, 222, 183, gives m.p. 104°).

Yield after recrystallisation 0.84 g. (26% based on acetylmandelyl chloride). Larger-scale hydrolyses gave poorer yields, even with ether extraction.

The product gave a yellow precipitate with ferric chloride, a deep red colour in the sodium nitroprusside test, and was acidic. It formed an oxime, a semicarbazone and a 2:4-dinitrophenylhydrazone. The oxime (m.p. 162 - 164°) was obtained by adding a solution of hydroxylamine hydrochloride in water to a solution of the ketone in N NaOH, allowing to stand for 24 hours and acidifying. The precipitate was recrystallised from ethyl acetate/light petroleum, when it gave a deep violet colour with ferric chloride. The semicarbazone and dinitrophenylhydrazone were obtained by normal methods.

\[
\text{C}_6\text{H}_5\text{CH(OC)}\text{OAc}_2\text{CO} + \text{CH}_3\text{C} = \text{NH}, \text{CHNa}.\text{COOE} (I) \rightarrow
\]

(1) **Acetylmandelyl chloride.**

This was prepared in 73% yield by the method already described.

(ii) **Ethyl \( \beta \)-aminocrotonate (I) (Mentzer et al., Bull. Soc. chim., 1945, 12, 161; cf. Tinker and Whatmough, J. Amer. Chem. Soc., 1952, 74, 5235).**

Ethyl acetoacetate (150 g., 1.15 mol.) was dissolved in dry ether (360 cc.) and ammonia was passed through the solution for four hours. A white crystalline precipitate appeared, and redissolved on standing overnight at room temperature. The solution was dried (\( \text{Na}_2\text{SO}_4 \)) and distilled under reduced pressure. The fraction with b.p. 109 - 111°/15 mm. (98 g., 66%) was collected (lit. m.p. 18°; Michaelis, Ann., 1909, 366, 337, gives b.p. 105°/15 mm.).
(iii) \(\alpha\)-Acetimido-\(\gamma\)-phenyltetronic acid (II).

A mixture of ethyl \(\beta\)-aminocrotonate (48 g., 0.37 mol.) in dry ether (175 ml.) and anhydrous pyridine (32.8 g., 0.42 mol.) was cooled to \(-50^\circ\) to \(-60^\circ\) in a dry ice/acetone bath. Acetymandelyl chloride (88.25 g., 0.42 mol.) in dry ether (80 ml.) was added to the reaction mixture over a period of two hours, with continuous stirring. The mixture was stirred continuously overnight while it was allowed to warm up to room temperature.

The product, a colourless solid, was shaken with chloroform (80 ml.) and water (200 ml.). The solid dissolved in the organic layer, which was separated, dried (\(\text{Na}_2\text{SO}_4\)) and distilled under reduced pressure, leaving a pale greenish-yellow resin which, on being shaken with a little dry ether, formed a white crystalline precipitate of the acetimido compound. This was collected and dried. (Yield 72 g., 89%.) Evaporation of solvent from the filtrate gave about 50 ml. of an oil which gave no further precipitate on treatment with ether. The acetimido compound was recrystallised from dry ether/40:60° petrol ether. M.p. 86 – 89° after one recrystallisation.

(iv) Hydrolysis to \(\alpha\)-acetyl-\(\gamma\)-phenyltetronic acid.

\(\alpha\)-Acetimido-\(\gamma\)-phenyltetronic acid (5.0 g., 0.023 mol.) was allowed to stand with 10% NaOH at room temperature for 24 hours. Acidification with dilute hydrochloric acid, filtration and extraction into chloroform were carried out.
The chloroform solution was shaken with sodium bicarbonate solution which was then acidified and extracted. The extract was dried ($\text{Na}_2\text{SO}_4$) and solvent removed under reduced pressure. The residual oil was crystallised from petrol-ether ($b. \ 60: 80^\circ$) (2.4 g., 48%). M.p. 102 - 104°.

Alkaline hydrolyses at temperatures above room temperature gave mainly neutral tars. Acid hydrolysis at room temperature, by shaking for 1 hour with dil. hydrochloric acid, similarly gave $\alpha$-acetyl-$\gamma$-phenyltetronic acid in 18% yield.

Sodium bisulphite compound: $\alpha$-Acetyl-$\gamma$-phenyltetronic acid (1 g.) was shaken with saturated aqueous sodium bisulphite (4 c.c.). No solution, precipitation or rise in temperature occurred. The mixture was warmed until solution was completed. The mixture solidified on cooling. The solid material was soluble in ether, insoluble in cold dilute HCl and was shown chromatographically to be $\alpha$-acetyl-$\gamma$-phenyltetronic acid (although R.N. Lacey (J., 1954, 532 - 539) says that $\alpha$-acetyl-tetronic acids readily form ketonic derivatives).

**CHROMATOGRAPHIC SEPARATION**

Using $\gamma$-phenyltetronic acid, standard $\alpha$-acetyl-$\gamma$-phenyltetronic acid, $\alpha$-bromo-$\gamma$-phenyltetronic acid, $\alpha\alpha$-dibromo-$\gamma$-phenyltetronic acid, benzoic acid and $\gamma$-phenyltetronic acid allyl ether a solvent was found which gave separations on Whatman No.1 paper and which would permit
estimation of the extent to which substitution reactions proceeded. The following solvent systems were used:

1) Water;

ii) A 5% aqueous solution of sodium acetate;

iii) isoPropanol/water (50:50, v./v.);

iv) isoPropanol/water (90:10, v./v.);

v) isoPropanol/glacial acetic acid/water (90:1:9, v./v.);

vi) nButanol/formic acid/water (85:5:10, v./v.);

ei) nButanol/pyridine/benzene/water (5:3:1:3, v./v.) (Tate and Lyle's solvent).

None of these solvents was found to give adequate separation, and in system (vi) all the materials were found to run at the solvent front. Two other solvent systems were found to give some separation, although α-disubstituted tetronic acids and tetronic acid enol ethers again ran at the solvent front; the enol esters ran as the acid anions.

viii) isoPropanol/ammonia (0.880/water (90:1:9, v./v.);

ix) nButanol/pyridine/ammonia (0.880)/sat. aqueous sodium chloride (40:80:30:50, v./v.).

This last solvent system, which was used by Bray, Lake, Thorpe and White (Biochem. J., 1950, 47, 13) for the separation of phenolic acids from the phenols and from each other in amounts of about 5 μg, was found to give satisfactory separation of several tetronic acids.

Contact prints were made of the dried papers using exposures of 2 - 3 seconds to a "Hanovia" lamp. R_p values
could then be obtained.

Table of Average R<sub>p</sub> values in Solvent System (ix).

<table>
<thead>
<tr>
<th>Substance</th>
<th>R&lt;sub&gt;p&lt;/sub&gt;</th>
<th>Substance</th>
<th>R&lt;sub&gt;p&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>γ-phentetronic acid</td>
<td>0.60</td>
<td>α-acetyl-γ-phentetronic acid</td>
<td>0.75</td>
</tr>
<tr>
<td>γγ-diphenyltetronic acid</td>
<td>0.67</td>
<td>α-bromo-γ-phentetronic acid</td>
<td>0.75</td>
</tr>
<tr>
<td>γ-methyltetronic acid</td>
<td>0.48</td>
<td>α-acetyl-γ-dimethyltetronic acid</td>
<td>0.74</td>
</tr>
<tr>
<td>γγ-dimethyltetronic acid</td>
<td>0.49</td>
<td>β-acetyl-γ-dimethyltetronic acid</td>
<td>0.74</td>
</tr>
<tr>
<td>2-benzoyl-γγ-dimethyltetronic acid</td>
<td>0.71</td>
<td>benzoic acid</td>
<td>0.45</td>
</tr>
<tr>
<td>γ-spirocyclhexyltetronic acid</td>
<td>0.60</td>
<td>α-acetyl-γγ-dimethyltetronic acid</td>
<td>0.61</td>
</tr>
<tr>
<td>2-methyltetronic acid</td>
<td>0.40</td>
<td>α-methyl-γ-spirocyclhexyltetronic acid</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td>α-benzoyl-γ-spirocyclhexyltetronic acid</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td></td>
<td>αγγ-trimethyltetronic acid</td>
<td>0.63</td>
</tr>
</tbody>
</table>

**FRIEDEL-CRAFTS ACYLATIONS.**

α-Acetyl-γ-phentetronic Acid.

γ-Phentetronic acid (13.2 g., 0.075 mol.) was mixed with acetyl chloride (75 ml.) and stannic chloride (26.1 g., 0.1 mol.) was added. Heat was evolved and the clear dark red solution was refluxed for 4 hours (CaCl₂ guard-tube) and then poured into ice-cold HCl (150 ml. of 5N). The mixture was allowed to stand until it reached room-temperature, and then a little inorganic material was removed by filtration. The solution was then extracted with chloroform (4 x 30 ml.) which was washed with saturated aqueous sodium hydrogen
carbonate. (At this stage, much inorganic material was removed with difficulty by filtration). The combined washings were acidified cautiously with concentrated hydrochloric acid, which produced a white opacity. This mixture was extracted with chloroform (4 x 30 ml.), and the extract was dried ($\text{Na}_2\text{SO}_4$) and distilled at reduced pressure.

A residue of a brown semi-crystalline material (6.8 g.) remained which gave a negative nitrite test and was shown chromatographically to consist of approximately 90% $\alpha$-acetyl-$\gamma$-phenyltetronic acid and 10% unchanged $\gamma$-phenyltetronic acid. (If approximately 50% of an unchanged tetronic acid is present in a mixture, a red or purple colour is obtained with aqueous sodium nitrite solution.) The original chloroform extract, with neutral content, was dried ($\text{Na}_2\text{SO}_4$) and distilled at reduced pressure and left a small residue of dark brown tar which was shown chromatographically to contain no acidic tetronic acids.

The conditions described appeared to be the most favourable. Refluxing for longer periods decreased the total recovery of acidic material; heating in nitrobenzene as solvent gave a recovery of 70% of acidic material but $\alpha$-acetyl-$\gamma$-phenyltetronic acid was present to an extent of only about 40% (nitrite test positive). Aluminium chloride and zinc chloride in acetyl chloride as solvent both allowed a recovery of 75% of acidic material but were estimated chromatographically
to have given only 50% and 70% conversion respectively. The use of $\gamma$-phenyltetronic acid enol acetate (prepared as detailed later) instead of the tetronic acid itself gave no increase in yield.

**Purification of $\alpha$-acetyl-$\gamma$-phenyltetronic acid.**

(a) By sublimation: $\alpha$-Acetyl-$\gamma$-phenyltetronic acid was found to sublime more readily than $\gamma$-phenyltetronic acid, but the difference was not enough to give complete separation.

(b) By crystallisation: Extraction of half of the crude semi-crystalline product, containing about 90% of $\alpha$-acetyl-$\gamma$-phenyltetronic acid, with hot light petroleum (b. 80 - 100°) followed by evaporation of the solvent left a yellow oil which partially crystallised. The liquid portion micro-distilled at about 50°/0.1 mm. but the distillate was found chromatographically still to contain some unchanged $\gamma$-phenyltetronic acid, as did the crystalline portion of the extract. The crystalline material was recrystallised 5 times from light petroleum (b. 60 - 80°) before it was found to be chromatographically and analytically pure. Yield 1.6 g. (20%). M.p. 101 - 104°; mixed m.p. with pure authentic specimen, 100 - 102°. R. N. Lacey (loc. cit.) gives m.p. 104 - 105°. (Found: C, 66.53; H, 4.74. Calc. for C$_{12}$H$_{10}$O$_4$: C, 66.05; H, 4.62%).
By methylation and chromatography: Diazomethane was prepared from \( p \)-tolylsulphophynethylmethylnitrosamide (5 g., 0.023 mol.) according to the method of de Boer and Backer (Rec. Trav. chim., 1954, 73, 229). An ethereal distillate was collected which would contain about 0.73 g. (0.017 mol., about 70%) diazomethane. The solution was dried over potassium hydroxide pellets.

The above solution was filtered into a suspension of a portion of the crude \( \alpha \)-acetyl-\( \gamma \)-phenyltetronic acid (3.4 g., about 0.016 mol.) in ether (50 ml.). Nitrogen was immediately evolved and the mixture set aside overnight. Filtration and evaporation of the ether in vacuo gave a red oil which was dissolved in benzene and transferred to a column of activated alumina. Elution with benzene yielded very slowly a fraction containing a substance (0.2 g.) which crystallised slowly on standing. After recrystallisation from ethyl acetate/light petroleum (b. 80 : 100°) its m.p. was 90 - 92° (m.p. of \( \gamma \)-phenyltetronic acid methyl ether 95°; mixed m.p., 90 - 92°). Further elution with ether/light petroleum (10:90, v./v.) gave no recovery. Chloroform afforded a further fraction (1.8 g.) of a yellow oil and ethanol gave some dark red oil. Neither of these fractions would crystallise.
(d) By formation of ketonic derivatives:

(i) **Phenyl hydrazones**: The crude \( \alpha \)-acetyl-\( \gamma \)-phenyltetronic acid (2 g.) was heated with phenylhydrazine (1.1 g.) for two minutes. The resultant brown material would not crystallise, and was transferred to a column of activated alumina and eluted with benzene. Two fractions of eluate were obtained, but only the second crystallised from ethanol. M.p. 156 - 157° (Lacey, **loc. cit.**, gives m.p. 157 - 158°).

(ii) **Bisulphite compound**: \( \alpha \)-acetyl-\( \gamma \)-phenyltetronic acid would not form a bisulphite compound (see p.121).

\( \alpha \)-Acetyl-\( \gamma \)-diphenyltetronic Acid.

\( \gamma \gamma \)-Diphenyltetronic acid (2.0 g., 0.008 mol.) was mixed with acetyl chloride (20 ml.) and stannic chloride (2.9 g., 0.011 mol.) was added and the mixture was refluxed for 12 hours. The brown mixture was worked up as before, chloroform extraction of acidified sodium bicarbonate washings allowing recovery of a brown crystalline solid (1.3 g., 56%) which was shown chromatographically to consist only of \( \alpha \)-acetyl-\( \gamma \gamma \)-diphenyltetronic acid with no unchanged \( \gamma \gamma \)-diphenyltetronic acid. The product crystallised readily from light petroleum (b. 60:80°), M.p. 99 - 101°; mixed m.p. with product obtained by Fries rearrangement, 99°. R. N. Lacey (**loc. cit.**) gives m.p. 102°.
**α-Acetyl-γ-methyltetronic Acid.**

γ-Methyltetronic acid (2.3 g., 0.02 mol.) was mixed with acetyl chloride (20 ml.) and stannic chloride (6.5 g., 0.025 mol.) was added. The mixture was refluxed for 2 hours and worked up as before. Chloroform and ethyl acetate extraction of acidified sodium bicarbonate washings yielded finally a brown oil (0.4 g.) which gave a positive nitrite test and was shown chromatographically to consist mainly of γ-methyltetronic acid with possibly a small amount of a faster-running substance (R<sub>t</sub> 0.6). After two crystallisations from ethyl acetate/light petroleum (b. 60:80°) the product had m.p. 113° (m.p. of γ-methyltetronic acid 115 - 117°).

**α-Acetyl-ω-dimethyltetronic Acid.**

ω-Dimethyltetronic acid (2.6 g., 0.02 mol.) was mixed with acetyl chloride (20 ml.) and stannic chloride (6.5 g., 0.025 mol.) was added. The mixture was refluxed for 4 hours and worked up as usual. (Two hours refluxing was found to give only about 70% conversion). Chloroform and ethyl acetate extracts of acidified sodium bicarbonate washings yielded finally a crystalline solid (2.0 g., 58%) which was shown chromatographically to contain little or no ω-dimethyltetronic acid. Crystallisation from light petroleum (b. 80:100°) gave pure α-acetyl-ω-dimethyltetronic acid, m.p. 64°. Mixed m.p., with product by Fries rearrangement, 64°. R. N. Lacey, (loc. cit.) gives m.p. 64 - 65°.
\(\alpha\)-Acetyl-\(\gamma\)-spirocyclohexyltetronic Acid.

\(\gamma\)-Spirocyclohexyltetronic acid (3.4 g., 0.02 mol.) was mixed with acetyl chloride (20 ml.) and stannic chloride (6.5 g., 0.025 mol.) was added. The mixture was refluxed for 4 hours and worked up as usual. Acidification of sodium bicarbonate washings gave a precipitate, and allowed extraction into chloroform of \(\gamma\)-spirocyclohexyltetronic acid. (m.p. after crystallisation 195°, nitrite test positive). Chromatography showed that no other acidic tetronic acid was present.

\(\alpha\)-Benzoyl-\(\gamma\)-phenyltetronic Acid.

(i) \(\gamma\)-Phenyltetronic acid (4.4 g., 0.025 mol.) was mixed with benzoyl chloride (30 ml.) and stannic chloride (8.6 g., 0.033 mol.) was added. The mixture was heated at 150° for 3 hours, the bulk of the benzoyl chloride was distilled off at reduced pressure, and the residue worked up as usual. Acidification of sodium bicarbonate washings allowed collection by filtration and by chloroform extraction of a substance consisting almost entirely of benzoic acid (chromatography). Sublimation of the benzoic acid at reduced pressure left a crystalline substance which proved to be mainly \(\gamma\)-phenyltetronic acid giving a positive nitrite test, but containing also about 20% of a faster-running substance \((R_p 0.8)\).

(ii) \(\gamma\)-Phenyltetronic acid (4.4 g., 0.025 mol.), benzoyl chloride (4.7 g., 0.033 mol.), and aluminium chloride
(4.5 g., 0.033 mol.) in dry nitrobenzene (40 ml.) were heated for 3 hours at 150°. The usual procedure gave only δ-phenyltetronic acid and benzoic acid. Similar treatment using stannic chloride as catalyst also gave only δ-phenyltetronic acid and benzoic acid.

(iii) δ-Phenyltetronic acid enol acetate (prepared by the method described later) (2.18 g., 0.01 mol.) and benzoyl chloride (1.9 g., 0.013 mol.) were mixed with dry nitrobenzene (20 ml.) and aluminium chloride (1.9 g., 0.013 mol.) was added. The mixture was heated at 150° for 2 hours and worked up as usual. The recovered acidic material consisted only of benzoic acid and δ-phenyltetronic acid.

δ-(α-Carboxypropionyl)-δ-phenyltetronic Acid. (Cf. "Organic Syntheses", Coll. Vol. XIII, 12, and XV, 92.)

δ-Phenyltetronic acid (5.9 g., 0.033 mol.) and succinic anhydride (3.3 g., 0.033 mol.) were mixed with dry nitrobenzene (35 ml.) and aluminium chloride (12.0 g., 0.088 mol.) was added, some heat being evolved. The mixture was heated at 100° for two hours, when it was gelatinous, and was allowed to stand overnight. Trituration with ice-cold hydrochloric acid (100 ml. of 50%), extraction into ether, washing with sodium bicarbonate solution, and acidification of the washings resulted in precipitation of a red viscous oil. The washings were extracted continuously for 18 hours with ethyl acetate,
the extract was dried and distilled at reduced pressure. A dark red resin (7.1 g.) remained, which partially crystallised on standing. This material gave a positive nitrite test, and gave two spots on a chromatogram representing $\gamma$-phenyllactonic acid (70%) and a faster-running substance (30%) ($R_f$ 0.76). (Succinic acid is not located by U.V. light absorption).

Crystallisation using ethyl acetate/light petroleum (b. 60:80°) gave two fractions consisting only of $\gamma$-phenyllactonic acid and succinic acid; later fractions all contained $\gamma$-phenyllactonic acid and another component, ($R_f$ 0.76) in equal amounts.

$\beta$-Nitrobenzyl ester:

The above crude product (1 g.) was added to water (5 ml.) and neutralised with 10% NaOH solution. This solution was made slightly acid with hydrochloric acid and added to a solution of $\beta$-nitrobenzyl bromide (1 g.) in alcohol (20 ml.) and the mixture boiled for 2 hours. The solution was allowed to cool, and since no crystals separated water was added. Two fractions of crystals separated after a time, with m.p. 139° and 144°; m.p. after recrystallisation from ethanol 143°. (Not analytically pure).

Carolinic Acid ($\alpha$-$(\beta$-carboxypropionyl)-$\gamma$-methyltetronic acid).

Method A:

$\gamma$-Methyltetronic acid (3.4 g., 0.03 mol.) and succinic anhydride (3.0 g., 0.03 mol.) were mixed with dry nitrobenzene (25 ml.) and aluminium chloride (12.0 g., 0.086 mol.) was added, heat being evolved. The mixture was heated for 4 hours
at 100° and then cooled and triturated with ice-cold hydrochloric acid (100 ml. of 50%). This solution was extracted continuously for 24 hours with ethyl acetate, and the extract washed with saturated sodium bicarbonate solution. The washings were acidified and continuously extracted with ethyl acetate for 24 hours. Drying (Na₂SO₄) and evaporation of solvent at reduced pressure gave a brown semi-crystalline material (4.9 g.). This was dissolved in hot A.R. acetone and a little light petroleum (b.80:100°) added. Crystals separated and were collected and found to melt at 181 - 182° (succinic acid m.p. 188°). They did not absorb U.V. light.

The crystallisation filtrate was evaporated down and the residue examined by paper chromatography using n-propanol/ammonia (0.880)/water (50:25:25, v/v/v.). When the paper had been irrigated for 20 hours, it was dried and sprayed with aqueous ferric chloride solution. Authentic dl-carolinic acid (synthesised by Dr. J. R. Plimmer), γ-methyltetronic acid and succinic acid were used for comparison. Carolinic acid (Rₚ 0.60) gave an orange spot against a pale yellow background. The residue showed only δ-methyltetronic acid (brown spot Rₚ 0.69) since succinic acid gives no colour with ferric chloride.
Method B:

(i) **Methyl hydrogen succinate** (Bone, Sudborough and Sprankling, J., 1904, 534; cf. Riegel and Lilienfeld, J. Amer. Chem. Soc., 1925, 47, 1273). To succinic anhydride (100 g., 1.0 mol.) was added dry methanol (64 g., 2.0 mol.). The mixture was refluxed for 0.75 hour, after which excess alcohol was removed. The residue crystallised from hot carbon disulphide, a small amount of insoluble succinic acid being removed by filtration. The acid half-ester (124 g., 93%) had m.p. 58° (lit. 58°).

(ii) **4-Methoxycarbonylpronionyl chloride** (Robinson and Robinson, J., 1925, 180). To the above methyl hydrogen succinate was added thionyl chloride (140 ml.) and the mixture was heated under reflux for 1.5 hours. When the solution had stood overnight excess thionyl chloride was removed by distillation under reduced pressure and the acid chloride (104 g., 73%) distilled as a colourless liquid b.p. 76 - 80°/12 mm., n_D^17 1.4400. Robinson and Robinson (loc. cit.) give b.p. 93°/18 mm.

(iii) **γ-Methyltetronic acid** (8.6 g., 0.075 mol.) was added to the above acid chloride (11.3 g., 0.075 mol.). Stannic chloride (26.1 g., 0.1 mol.) was added causing evolution of heat and darkening in colour. The mixture was heated at 100° for 2 hours, and worked up as described for the succinic anhydride experiment. Continuous extraction with ethyl acetate of acidified sodium bicarbonate washings and drying and distillation of the extract gave a semicrystalline oil (12.0 g.). Crystallisation from ethyl acetate gave chromatographically pure succinic acid, m.p. 185° (succinic acid m.p. 188°). The crystallisation
filtrate was evaporated and the residue examined by paper chromatography using propanol/ammonia (0.880)/water (50:25:25, v/v/v.). A small spot (R_f 0.60), representing about 5 - 10% of the whole, corresponding exactly to the standard authentic carolinic acid was shown up by spraying the dried paper with aqueous ferric chloride solution.

FRIEDEL-CRAFTS ALEYLATIONS.

_α_-Ethyl-γ-phenyltetronic Acid.

To a suspension of γ-phenyltetronic acid (4.4 g., 0.025 mol and redistilled ethyl bromide (25 ml.) was added stannic chloride (8.7 g., 0.033 mol.). The mixture was refluxed for 2 hours and worked up as described for acylations. No neutral material was left when ethyl bromide was distilled from the original washed extract. The acidic product obtained gave a positive nitrite test, and was found chromatographically to be pure γ-phenyltetronic acid. After recrystallisation from ethyl acetate it had m.p. 124° (γ-Phenyltetronic acid m.p. 126°).

_α_-Benzyl-γ-phenyltetronic Acid.

To a suspension of γ-phenyltetronic acid (4.4 g., 0.025 mol.) in redistilled benzyl chloride (25 ml.) was added aluminium chloride (4.5 g., 0.033 mol.). The mixture was heated for 2 hours at 150°, although it became solid after the first 10 minutes, and then triturated with ice-cold hydrochloric acid (100 ml. of 50%). Inorganic solid material was filtered off, the solution was extracted with chloroform, and the extract was washed with saturated sodium bicarbonate solution.
Acidification of the washings precipitated crystalline J-phenyltetronic acid (3.6 g.). Extraction of the mother-liquor with chloroform gave no further recovery.

**FRIES REARRANGEMENTS.**

**Preparation of Enol Esters.**

**J-Phenyltetronic acid enol acetate.**

J-Phenyltetronic acid (13.2 g., 0.073 mol.) was ground with acetic anhydride (35 ml.). Concentrated sulphuric acid (4 drops) was added and the reaction was allowed to proceed at room temperature for 2 hours. The solution was then diluted with chloroform (150 ml.) and washed with saturated sodium bicarbonate solution. The chloroform layer was dried (Na$_2$SO$_4$) and evaporated under diminished pressure. The residual light brown oil solidified. The enol acetate of J-phenyltetronic acid thus obtained (11.8 g., 81%) crystallised from light petroleum (b. 60 - 80°) as needles m.p. 79°. J. R. Flimmer (Ph.D. Thesis, Edinburgh, 1955, p.113) gives m.p. 79°.

**Jk-Diphenyltetronic acid enol acetate.**

To Jk-diphenyltetronic acid (12.6 g., 0.05 mol.) and acetic anhydride (35 ml.) sulphuric acid (4 drops) was added and the solution was allowed to stand overnight. Chloroform (150 ml.) was added and this solution was washed with saturated sodium bicarbonate solution, from which Jk-diphenyltetronic acid (1.1 g.) was precipitated by acidification and collected. The neutral chloroform solution was dried (Na$_2$SO$_4$) and
evaporated under diminished pressure. The residual oil was extracted into light petroleum (b. 80 - 100°) from which it crystallised readily in needles, m.p. 105°. This was the enol acetate of \( \alpha \alpha \)-diphenyltetronic acid (10.0 g., 68%).

(Found: C, 73.56; H, 4.67. \( \text{C}_{18} \text{H}_{14} \text{O}_{4} \) requires C, 73.46; H, 4.80%).

\( \alpha \alpha \)-Dimethyltetronic acid enol acetate.

To \( \alpha \alpha \)-dimethyltetronic acid (12.8 g., 0.1 mol.) and acetic anhydride (35 ml.) sulphuric acid (4 drops) was added and the solution was allowed to stand overnight. The procedure detailed above was followed, and yielded an oil which crystallised readily as plates from light petroleum (b. 80 - 100°) m.p. 59 - 60°. This was the enol acetate of \( \alpha \alpha \)-dimethyltetronic acid (13.4 g., 79%). (Found: C, 56.67; H, 6.24. \( \text{C}_{6} \text{H}_{10} \text{O}_{4} \) requires C, 56.46; H, 5.92%)

\( \gamma \)-Spirocyclohexyltetronic acid enol acetate.

To \( \gamma \)-spirocyclohexyltetronic acid (8.4 g., 0.05 mol.) in acetic anhydride (20 ml.) sulphuric acid (3 drops) was added, and the mixture was warmed in a water-bath for 1 minute and allowed to stand at room temperature overnight. The procedure detailed above resulted in a semi-crystalline oil which crystallised readily as plates from light petroleum (b. 60 - 80°) m.p. 93°. This was the enol acetate of \( \gamma \)-spirocyclohexyltetronic acid (7.8 g., 74%). (Found: C, 63.08; H, 6.83. \( \text{C}_{11} \text{H}_{14} \text{O}_{4} \) requires C, 62.85; H, 6.71%).
**γ-Phenyltetronic acid enol benzoate.**

γ-Phenyltetronic acid (13.2 g., 0.075 mol.) was dissolved in sodium carbonate (500 ml.) and the solution was shaken in a stoppered flask with benzoyl chloride (10.6 g., 0.075 mol.) for 0.5 hour. The mixture was allowed to stand for 3 days and a brown resin was collected by filtration, washed with sodium carbonate solution, and dried over P₂O₅. Crystallisation from light petroleum (b. 80 - 100°) gave γ-phenyltetronic acid enol benzoate (14.5 g., 69%), m.p. 93°. (Found: C, 73.28; H, 4.56; C₁₇H₁₂O₄ requires C, 72.83; H, 4.32%).

**γγ-Diphenyltetronic acid enol benzoate.**

γγ-Diphenyltetronic acid (12.6 g., 0.05 mol.) and benzoyl chloride (7.0 g., 0.05 mol.) were treated as detailed above. The neutral resin was crystallised from light petroleum (b. 80 - 100°) to give γγ-diphenyltetronic acid enol benzoate (13.5 g., 76%), m.p. 165°. (Found: C, 77.58; H, 4.56; C₂₅H₁₆O₄ requires C, 77.49; H, 4.52%).

**γ-Methyltetronic acid enol benzoate.**

γ-Methyltetronic acid (11.4 g., 0.1 mol.) and benzoyl chloride (14.0 g., 0.1 mol.) were treated as detailed above. The neutral resin was crystallised from light petroleum (b. 60 - 80°) to give γ-methyltetronic acid enol benzoate (13.5 g., 68%) m.p. 39 - 40°. (Found: C, 65.85; H, 4.54; C₁₂H₁₀O₄ requires C, 66.05; H, 4.62%).
**δδ-Dimethyltetronic acid enol benzoate.**

δδ-Dimethyltetronic acid (12.8 g., 0.1 mol.) and benzoyl chloride (14.0 g., 0.1 mol.) were treated as detailed above. The neutral resin was crystallised from light petroleum (b. 80 - 100°) to give δδ-dimethyltetronic acid benzoate (16.9 g., 75%) m.p. 130 - 131°. (Found: C, 66.94; H, 4.99. C_{13}H_{12}O_4 requires C, 67.23; H, 5.21%).

**δ-Spirocyclohexyltetronic acid enol benzoate.**

δ-Spirocyclohexyltetronic acid (8.4 g., 0.05 mol.) and benzoyl chloride (7.0 g., 0.05 mol.) were treated as detailed above. The neutral resin was crystallised from light petroleum (b. 80 - 100°) to give δ-spirocyclohexyltetronic acid benzoate (11.2 g., 82%), m.p. 125°. (Found: C, 71.02; H, 5.90. C_{16}H_{16}O_4 requires C, 70.56; H, 5.92%).

**Rearrangement of Enol Esters.**

**δ-Phenyltetronic acid enol acetate.**

(1) To a suspension of the ester (2.2 g., 0.01 mol.) in dry nitrobenzene (10 ml.) was added aluminium chloride (1.9 g., 0.013 mol.). The mixture was heated at 60° for 0.25 hour and allowed to stand at room temperature for 18 hours. It was then poured into ice-cold hydrochloric acid (30 ml. of 50%), some inorganic material was removed and the solution was extracted into ether. The ether extract was washed with saturated sodium bicarbonate solution and the washings were acidified. The precipitate which separated
(1.6 g.) gave a positive nitrite test and m.p. 127°. Mixed m.p. with \( \gamma \)-phenyltetronic acid, 126°. It ran as pure \( \gamma \)-phenyltetronic acid on a paper chromatogram.

Varying proportions of ester and aluminium chloride were reacted at other temperatures in nitrobenzene and carbon disulphide (removed before further heating) as solvents. The results are tabulated:

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3 equiv.</td>
<td>Nitrobenzene</td>
<td>60°/0.25 hour, 20°/18 hours.</td>
<td>( \gamma )-phenyltetronic acid only.</td>
</tr>
<tr>
<td>1.3 equiv.</td>
<td>Nitrobenzene</td>
<td>150°/0.25 hour, 20°/18 hours.</td>
<td>70% recovery consisting of - 5% ( \alpha )-acetyl-( \gamma )-phenyltetronic acid 95% ( \gamma )-phenyltetronic acid.</td>
</tr>
<tr>
<td>2.0 equiv.</td>
<td>CS(_2) then none.</td>
<td>46°/3 hours, 100°/0.5 hour.</td>
<td>( \gamma )-phenyltetronic acid only.</td>
</tr>
</tbody>
</table>

(ii) To a suspension of the ester (2.2 g., 0.01 mol.) in dry nitrobenzene (10 ml.) was added stannic chloride (3.5 g., 0.013 mol.). The mixture was heated at 100° for 2.5 hours and worked up as usual. Dark brown semi-crystalline material (1.7 g.) was obtained which gave a positive nitrite test and was found chromatographically to contain \( \alpha \)-acetyl-\( \gamma \)-phenyltetronic acid and \( \gamma \)-phenyltetronic acid in equal amounts.
(iii) A mixture of the ester (2.2 g., 0.01 mol.), dry nitrobenzene (10 ml.) and anhydrous zinc chloride (freshly-ground) (1.81 g., 0.013 mol.) was heated at 100° for 2.5 hours and allowed to stand overnight at room temperature. The mixture was worked up as usual, giving a brown crystalline material (2.0 g.) with weak positive nitrite test, containing about 75% \( \alpha \)-acetyl-\( \gamma \)-phenyltetronic acid and 25% \( \gamma \)-phenyltetronic acid.

A similar experiment, but involving heating for 4 hours resulted in a total recovery of 1.1 g., with negative nitrite test and containing about 10% of \( \gamma \)-phenyltetronic acid. This material was run on 10 chromatograms of 3 mm. Whatman No.1 paper, the papers were dried and the products located photographically on each paper. The appropriate areas were cut out and continuously eluted with petrol ether (b. 60 - 80°), which gave no solid eluate. The papers were lightly sprayed with dilute hydrochloric acid and eluted continuously with ethanol. Evaporation of the solvent left yellow crystals (500 mg.) which were crystallised twice from petroleum ether (b. 60 - 80°) m.p. 104 - 106°. Mixed m.p. with standard \( \alpha \)-acetyl-\( \gamma \)-phenyltetronic acid, 104 - 105°. This material ran as the pure \( \alpha \)-acetyl compound on a paper chromatogram and gave a negative nitrite test.

\( \gamma \)-Diphenyltetronic acid enol acetate.

(i) A mixture of the ester (2.9 g., 0.01 mol.), dry nitrobenzene (10 ml.) and anhydrous freshly ground zinc chloride (1.81 g., 0.013 mol.) was heated at 100° for 2 hours and worked up as usual.
Crystals (2.4 g.) precipitated by acidification of the bicarbonate washings were found to be pure αβ-diphenyltetronic acid. M.p. after crystallising from ethanol 209 - 210° (αβ-diphenyltetronic acid m.p. 212°).

(ii) A similar experiment but using aluminium chloride as catalyst and heating for 5 hours gave a product (1.7 g.) by ethereal extraction which contained 90% of the α-acetyl compound and 10% αβ-diphenyltetronic acid. Crystallisation from light petroleum (60 - 80°) gave the α-acetyl-αβ-diphenyltetronic acid, m.p. 99°. Mixed m.p. with product of Friedel-Crafts reaction, 99°.

(iii) When stannic chloride (0.013 mol.) was used as catalyst, with heating for 5 hours, complete conversion to α-acetyl-αβ-diphenyltetronic acid (1.85 g., 63%) was achieved. M.p. 99 - 100°. (Found: C, 73.76; H, 5.02. Calc. for C18H14O4: C, 73.48; H, 4.86%)

γ-Methyltetronic acid enol acetate.

A mixture of the crude ester (1.56 g., 0.01 mol.) was treated as before with stannic chloride for 3 hours. The recovered acidic material contained about 50% of a new material (Pf 0.49). This crude material in boiling benzene with phenylhydrazine gave a phenylhydrazone m.p. 164 - 165° (Lacey, loc. cit., gives m.p. 165°).

γγ-Dimethyltetronic acid enol acetate.

A mixture of the ester (1.7 g., 0.01 mol.), dry nitrobenzene (10 ml.) and stannic chloride (3.5 g., 0.013 mol.) was heated at 100° for 2 hours and worked up as usual. Extraction
with ethyl acetate of the acidified bicarbonate washings, drying (Na$_2$SO$_4$) and removal of the solvent at reduced pressure gave α-acetyl-γ-γ-dimethyltetronic acid (1.2 g., 71%), m.p. 64° after recrystallisation from light petroleum (b. 60 - 80°). Mixed m.p. with product of Friedel-Crafts reaction, 64°. (Found: C, 56.95; H, 6.11. Calc. for C$_8$H$_{10}$O: C, 56.46; H, 5.92%)

**γ-Spirocyclohexyltetronic acid enol acetate.**

A mixture of the ester (2.1 g., 0.01 mol.), dry nitrobenzene (10 ml.), and stannic chloride (3.5 g., 0.013 mol.) was heated at 100° for 2 hours and worked up as usual. Acidification of the bicarbonate washings precipitated crystals (1.5 g.) of γ-spirocyclohexyltetronic acid, which was chromatographically pure.

**γ-Phenyltetronic acid enol benzoate.**

A mixture of the ester (2.8 g., 0.01 mol.), dry nitrobenzene (10 ml.) and stannic chloride (3.5 g., 0.013 mol.) was heated at 100° for 4 hours and worked up as usual. Acidification of the bicarbonate washings, filtration and also ethereal extraction gave a crystalline material (2.6 g.) which gave a negative nitrite test and was found chromatographically to consist mainly of benzoic and γ-phenyltetronic acids but to contain about 10% of a third substance (R$_p$ 0.79).

**γγ-Diphenyltetronic acid enol benzoate.**

A mixture of the ester (3.6 g., 0.01 mol.), dry nitrobenzene (10 ml.) and stannic chloride (3.5 g., 0.013 mol.)
was heated at 100° for 4 hours and worked up as usual. Acidification of the bicarbonate washings allowed collection of crystalline material (3.1 g.) with a negative nitrite test, consisting of approximately 30% benzoic acid, 20% \( \alpha \alpha \)-diphenyltetronic acid, and 50% of a third substance \( (R_p 0.82) \). Removal by sublimation of the benzoic acid, followed by crystallisation of the residue in light petroleum (b. 80 - 100°) gave no separation of the \( \alpha \)-benzoyl compound from the \( \alpha \alpha \)-diphenyltetronic acid. The crude product would not form a semicarbazone.

A similar experiment using zinc chloride (0.013 mol.) as catalyst gave no conversion to the \( \alpha \)-benzoyl compound. \( \alpha \)-Methyldtetronic acid enol benzoate.

A similar experiment using the ester (2.18 g., 0.01 mol.) dry nitrobenzene (10 ml.), and stannic chloride (3.5 g., 0.013 mol.) gave only benzoic acid (0.9 g.) containing no tetronic acid. \( \alpha \alpha \)-Dimethyldtetronic acid enol benzoate. A mixture of the ester (2.3 g., 0.01 mol.), dry nitrobenzene (10 ml.) and stannic chloride (3.5 g., 0.013 mol.) was heated at 100° for 4 hours and worked up as usual. Acidification of the bicarbonate washings followed by extraction into ethyl acetate and drying (\( Na_2SO_4 \)) and evaporation of the solvent left \( \alpha \)-benzoyl-\( \alpha \alpha \)-dimethyldtetronic acid (1.8 g., 77%) m.p. 77° after recrystallisation from light petroleum (b. 80 - 100°). (Found: C, 67.15; H 5.23.
\[ C_{13}H_{12}O_4 \] requires C, 67.19; H, 5.22%.

\( \gamma \)-Spirocylohexyltetronic acid enol benzoate.

A similar experiment using the ester (2.7 g., 0.01 mol.), dry nitrobenzene (10 ml.), and stannic chloride (3.5 g., 0.013 mol.) gave, by filtration of the acidified bicarbonate washings, what was probably \( \alpha \)-benzoyl-\( \gamma \)-spirocylohexyltetronic acid (1.9 g., 71%), m.p. 119° after recrystallisation from ethyl acetate/light petroleum (b. 80 - 100°). \( R_f \) value 0.78 with solvent system (ix).

HOSCH REACTION.

3-Acetimido-5-phenyltetronic acid hydrochloride.

3-Acetimido-5-phenyltetronic acid (2 g.) (prepared as on p.120) was dissolved in dry ether (20 ml.) and the solution was saturated with dry hydrogen chloride, when it became orange. Evaporation of solvent left a yellow oil which crystallised from dry ether/light petroleum (b. 40 - 60°). m.p. 87 - 88°. (M.p. of \( \alpha \)-acetimido-\( \gamma \)-phenyltetronic acid 86 - 89°).

\( \gamma \)-Phenyltetronic acid ethyl ether.

\( \gamma \)-Phenyltetronic acid (2.6 g., 0.015 mol.) was dissolved in dry ethyl acetate (100 ml.). The solution was saturated with dry hydrogen chloride and allowed to stand for 24 hours, and then washed with water and saturated aqueous sodium bicarbonate, from which \( \gamma \)-phenyltetronic acid (0.5 g.) was recovered by acidification. Drying and evaporation of the ethyl acetate gave yellow crystals (1.9 g., 61%) of
\( \gamma \)-phenyltetronic acid ethyl ether, which recrystallised from light petroleum (b. 60 - 80\(^0\)) as long plates, m.p. 64\(^0\).

(Found: C, 70.55; H, 5.99. \( \text{C}_{12}\text{H}_{12}O_3 \) requires C, 70.57; H, 5.92\%). The U.V. light absorption spectrum in ethanol showed a slight inflection at \( \lambda_{\text{max}} \) 2570 \( \AA \) (\( \log E \geq 2.4 \)); at 2200 \( \AA \) it had \( \log E \leq 4.1 \).

Hoesch reaction.

(1) \( \gamma \)-Phenyltetronic acid (2.6 g., 0.015 mol.) was dissolved in freshly dried and distilled ethyl acetate (150 ml.), and zinc chloride (2.0 g., 0.015 mol.) and freshly-distilled acetonitrile (0.6 g., 0.015 mol.) were added. The mixture was kept at 0\(^0\) while it was saturated with dry hydrogen chloride. After standing for 24 hours the mixture was washed with water and aqueous sodium bicarbonate. The water washings were made just alkaline with dil. sodium hydroxide solution and heated in a water-bath for 1.5 hours, and then were cooled, acidified and extracted with ether. Drying and evaporation of the ether left chromatographically pure crystalline \( \gamma \)-phenyltetronic acid (positive nitrite test) (0.2g.) with no \( \alpha \)-acetyl compound. Acidification of the bicarbonate washings also precipitated only \( \gamma \)-phenyltetronic acid (1.1 g.).

The ethyl acetate layer was dried and distilled at reduced pressure, leaving a red crystalline material (1.2 g.) which sublimed and crystallised from light petroleum (b. 60 - 80\(^0\)), m.p. 64\(^0\). (Mixed m.p. with authentic ethyl ether above, 63 - 64\(^0\)). The crude neutral residue (0.5 g.)
was warmed for 2 hours at 60° with aqueous sodium hydroxide (20 ml. of 10%). The mixture was washed with ether and then acidified and extracted into ether. This extract was dried and distilled at reduced pressure leaving a residue (0.3 g.) which ran as \( \gamma \)-phenyltetronic acid only on a chromatogram.

(ii) To a suspension of \( \gamma \)-phenyltetronic acid (2.6 g., 0.015 mol.) ether (150 ml.), zinc chloride (2.0 g., 0.015 mol.) and acetonitrile (0.6 g., 0.015 mol.) were added, causing solution of the \( \gamma \)-phenyltetronic acid. Dry hydrogen chloride was passed in for 6 hours while the mixture was kept at 0°. Some orange oil and colourless crystals were deposited. The supernatant ether was decanted and after standing overnight at 0° it had deposited more oil. The oil was separated from the ether, and the ether was washed with aqueous bicarbonate. Acidification of the washings precipitated \( \gamma \)-phenyltetronic acid (1.4 g.) which was found to be chromatographically pure. The ether layer was dried and distilled leaving colourless crystals (0.2 g.) m.p. 74 - 76° (\( \gamma \)-phenyltetronic acid enol acetate m.p. 79°) which ran on a paper chromatogram as \( \gamma \)-phenyltetronic acid. Half of the original orange oil was dissolved in water (10 ml.) and heated at 80° for 1 hour. Cooling deposited crystals of chromatographically pure \( \gamma \)-phenyltetronic acid. Another portion of the oil was dissolved in water and the solution was neutralised carefully with solid \( \text{NaHCO}_3 \) and extracted with ether. The ether was dried and distilled leaving a little brown oil
which did not absorb U.V. light. Acidification of the bicarbonate layer, extraction with ether, and drying and distillation of the ether left only traces of brown oil which contained some \( \gamma \)-phenyltetronic acid.

(iii) The crystalline hydrochloride of acetonitrile was obtained by passing dry hydrogen chloride into an ethereal solution of freshly-distilled acetonitrile for 0.5 hour and evaporating the ether.

\( \gamma \)-Phenyltetronic acid (1.6 g., 0.01 mol.), acetonitrile hydrochloride (1 g., 0.014 mol.) and zinc chloride (1.9 g., 0.014 mol.) were added to dry nitrobenzene (10 ml.) and the mixture was heated at 120° for 0.5 hour and then poured into ice-cold water (100 ml.). This mixture was extracted with ether, the ether extract was washed with aqueous bicarbonate, and the bicarbonate washings were acidified. \( \gamma \)-Phenyltetronic acid (1.6 g.) separated. No \( \alpha \)-acetyl compound could be detected chromatographically.

**TETRONIC ACID ALLYL ETHERS: PREPARATION AND REARRANGEMENT.**

**\( \gamma \)-Phenyltetronic acid allyl ether (Williamson's method).**

To a stirred solution of sodium (1.7 g., 0.075 g. atom) in absolute ethanol (50 ml.) was added \( \gamma \)-phenyltetronic acid (8.8 g., 0.05 mol.). The mixture was stirred until solution was complete, and freshly-distilled allyl bromide (12.1 g., 0.1 mol.) was added, a cream-coloured precipitate appearing in 2 - 3 minutes. The mixture was heated under reflux on a water-bath for 5 hours and cooled, sodium bromide (7.3 g.)
was removed by filtration and washed with ether, and the yellow filtrate was poured into water (100 ml.) The heavy red oil which was precipitated was extracted into ether (5 x 40 ml.). The extract was washed with aqueous sodium hydrogen carbonate and water, dried (Na$_2$SO$_4$) and evaporated at reduced pressure to give a red oil (5.7 g., 81%) with negative nitrite and ferric chloride tests. Extraction and crystallisation from light petroleum (b. 40 – 60°) gave pure γ-phenyltetronic acid allyl ether, m.p. 46°.

(Found: C, 71.90; H, 5.57. C$_{13}$H$_{12}$O$_3$ requires: C, 72.19; H, 5.59%). In ethanol the substance showed $\lambda_{max}$ 2170 $\AA$ ($\log \varepsilon$ 4.21); cf. γ-phenyltetronic acid methyl ether with $\lambda_{max}$ 2200 $\AA$, $\log \varepsilon$ 4.22.

The crude uncrystallised oil could be distilled with difficulty at 82 – 88°/0.01 mm. (bath temperature 200°), $n_D^1$ 1.5200. The distillate did not crystallise (Found: C, 70.17; H, 6.84%), and a large distillation residue remained. The distillate was insoluble in sodium bicarbonate solution, and showed $\lambda_{max}$ 2580 $\AA$ ($\log \varepsilon$ 2.82).

Acidification and extraction of the sodium hydroxide and bicarbonate washings allowed recovery of γ-phenyltetronic acid (0.6 g.) with positive (purple) nitrite test.

**Hydrolyses:**

(i) The pure crystalline allyl ether (0.5 g.) was heated under reflux for 2 hours with aqueous sodium hydroxide solution (50 ml. of 10%). The cooled solution was extracted with ether,
and the extract dried and evaporated leaving a negligible residue. The alkaline layer was acidified and extracted with ether. Drying and evaporation of the extract left a brown oil (0.3 g.) with positive nitrite test, chromatographically identifiable as \( \gamma \)-phenyltetronic acid.

(ii) The distillate from the allyl ether (2 g.) was heated under reflux with hydrochloric acid (20 ml. of 0.2 N) for 5 hours, when about 25% of the oil remained undissolved. The mixture was cooled and extracted with ether, the ether extract was washed with bicarbonate solution, dried and evaporated at reduced pressure leaving some unchanged oil (0.8 g.). The bicarbonate washings were acidified and extracted with ether, the extract was dried and evaporated at reduced pressure leaving a crystalline residue (1.0 g.) which gave a negative nitrite test and a yellow colour with ferric chloride. It recrystallised from ethyl acetate as plates, m.p. 102 - 105° (mixed m.p. with \( \gamma \)-phenyltetronic acid, 89°). In ethanol it showed \( \lambda_{\text{max}} \) 2590 Å, log \( \varepsilon \) 3.42. The crude hydrolysate was found chromatographically to contain approx. 30% of \( \gamma \)-phenyltetronic acid with some faster-running material.

\[ \gamma \text{-Phenyltetronic acid \( p \)-propyl ether.} \]

(1) \( \gamma \)-Phenyltetronic acid allyl ether (1.0 g.) was dissolved in ethyl acetate and 5% Pd/BaSO\(_4\) catalyst (20 mg.) added. The mixture was shaken with hydrogen at atmospheric pressure until the calculated volume of hydrogen had been absorbed. Filtration and removal of solvent left the
\( \gamma \)-phenyltetronic acid \( n \)-propyl ether, m.p. 48 - 49°

from aqueous ethanol (Found: C, 70.6; H, 6.2.

\( \text{C}_{13} \text{H}_{14} \text{O}_{3} \) requires: C, 71.5; H, 6.5%).

(ii) (with S.P.G. Melrose). Using sodium (0.77 g.,

0.033 g. atom), absolute ethanol (30 ml.), \( \gamma \)-phenyltetronic acid (4.4 g., 0.025 mol.), and \( n \)-propyl bromide (6.2 g.,

0.05 mol.) and heating for 18 hours, Williamson's method
gave the \( \gamma \)-phenyltetronic acid \( n \)-propyl ether (0.4 g., 7%)
m.p. 48 - 49° from aqueous ethanol (mixed m.p. with
previous specimen, 48°). Both specimens showed slight
inflection at \( \lambda \) 2840 A, \( \log \varepsilon 3.3 \), in ethanol.

\( \alpha \alpha \)-Diphenyltetronic acid allyl ether.

Using sodium (1.7 g., 0.075 g. atom), absolute ethanol
(50 ml.) \( \alpha \alpha \)-diphenyltetronic acid (12.6 g., 0.05 mol.)
and allyl bromide (15 g., 0.13 mol.) the above procedure was
repeated, heating being continued for 18 hours. The neutral
oil obtained (12.3 g., 84%), which was crude \( \alpha \alpha \)-diphenyltetronic acid allyl ether, crystallised on standing, m.p. 93° approx.

It would not distil or sublime below 170°/0.1 mm., and was
not readily recrystallisable.

\( \alpha \alpha \)-Dimethyldetric acid allyl ether.

Using sodium (1.7 g., 0.075 g. atom), absolute ethanol
(50 ml.), \( \alpha \alpha \)-dimethyldetric acid (6.4 g., 0.05 mol.)
and allyl bromide (15 g., 0.13 mol.) the above procedure was
repeated, heating being continued for 14 hours. The neutral
oil obtained (6.7 g., 80%) was subjected to short-path distillation (b.p. 45°/0.3 mm. approx.) to give pure \( \delta \)-dimethyltetronic acid allyl ether, m.p. 20 - 22°.

(Found: C, 63.96; H, 7.21. \( \text{C}_9\text{H}_{12}\text{O}_3 \) requires: C, 64.27; H, 7.19%).

Rearrangements.

The allyl ether (2.0 g.) was mixed with ammonium chloride (2.0 g., 3 mol. equiv. approx.) and heated for 18 hours at 120°/0.01 mm. in a "cold finger" sublimation apparatus. The resulting mixture was triturated with aqueous sodium bicarbonate solution and chloroform. Drying and evaporation of the chloroform layer gave a small recovery (20 - 30%) of unchanged ether. Acidification of the aqueous bicarbonate layer, extraction into ether and drying and evaporation of the extract gave oils (1.0 - 1.5 g.) which were examined chromatographically using solvent system (ix), with the following results. The crude product from the ether of \( \delta \)-phenyltetronic acid showed about 20% conversion to a new substance; that from \( \alpha \alpha \)-diphenyltetronic acid ether contained about 50% of a new substance; while that from \( \delta \delta \)-dimethyltetronic acid ether contained about 95% of a new product. In each case the new product showed a higher \( R_p \) value than the parent tetronic acid.

The first two products could not be purified by crystallisation or sublimation. The crude \( \delta \delta \)-dimethyltetronic acid derivative gave a negative nitrite test. This product
would not crystallise and hydrogenation in presence of Adams' catalyst resulted in uptake of approximately the calculated amount of hydrogen, but the reduced product would not crystallise either. The crude rearrangement product did sublime at $150^\circ/0.01$ mm. to a crystalline solid (m.p. 85 - 87°) which was recrystallised from light petroleum (b. 80 - 100°) to give what was probably the pure $\alpha$-allyl-$\alpha$-dimethyltetronic acid (m.p. 89 - 90°). This material showed $\lambda_{\text{max}}^\circ$ 2550 $\AA$, $\log \varepsilon$ 4.85 in ethanol.

Attempted $\text{G}$-alkylation. (Cf. Stetter and Dierichs, Ber., 1952, 85, 61; Chem. Abs., 1953, 47, 12228).

To a solution of $\delta$-phenyltetronic acid (8.8 g., 0.05 mol.) in aqueous potassium hydroxide solution (11 ml. of 20%), copper powder (0.15 g.) and allyl bromide (6.7 g., 0.055 mol.) were added. The brown mixture was stirred for 3 hours and allowed to stand overnight when it was greenish yellow. The mixture was diluted with sodium hydroxide solution (100 ml. of 5%), copper was removed by filtration and the solution was washed with ether. Cautious acidification with dilute hydrochloric acid to pH4 precipitated a yellow oil and crystals. This product (2.0 g., 18%) was collected, dried and crystallised from light petroleum (b. 80 - 100°), m.p. 143 - 145°.

Further acidification of the aqueous solution to pH2 precipitated unchanged $\delta$-phenyltetronic acid (5.3 g.).
The product gave a negative nitrite test and was chromatographically distinct ($R_F$ 0.64) from $\gamma$-phenyltetronic acid ($R_F$ 0.60). Found: C, 62.04; H, 4.48; and O, 61.35; H, 4.72%. Active hydrogen content, 1.01%. 

$C_{13}H_{12}O_3$ requires: C, 72.21; H, 5.59%.

$\alpha$-Hydroxy-$\gamma$-phenyltetronic acid requires: C, 62.50; H, 4.2; active hydrogen content, 1.04%.

The compound showed $\lambda_{\text{max}}$, 2500, $\log \varepsilon$ 4.15 in ethanol. It gave a positive ene-diol test (a strong purple colour with 2-dinitrobenzene in saturated aqueous solution with a few drops of alkali) (Fearon and Kawerau, Biochem. J., 1943, 37, 326). 5 mg. of the compound and of $\gamma$-phenyltetronic acid were added to portions of saturated aqueous bicarbonate solution, hydrochloric acid, and dilute acetic acid and each solution was tested with both permanganate and iodine in potassium iodide solution. Little difference was found between the substance and the parent tetronic acid in reducing properties, both being most active in bicarbonate solution.

Attempts to obtain crystalline acetyl derivatives by means of acetic anhydride/conc. sulphuric acid and acetyl chloride/pyridine were unsuccessful, both methods giving a small amount of neutral oil which would not crystallise, and a good recovery of unchanged acidic material.
**DIAZO-COUPLING**

**α-Benzeneazo-γ-phenyltetronic acid.**

Aniline (9.3 g., 0.1 mol.) was dissolved in hydrochloric acid (120 ml. of 2 N) and the solution was cooled to 5°. Sodium nitrite (10.4 g., 0.15 mol.) in water (20 ml.) was added gradually while the solution was stirred. γ-Phenyltetronic acid (17.6 g., 0.1 mol.) dissolved in aqueous potassium carbonate solution (30 g., in 75 ml.) was added slowly, while stirring and cooling were continued. The yellow product which separated was collected (17.5 g., 66%) and crystallised from ethanol (m.p. 125°) and glacial acetic acid (m.p. 118–120°, purple) as α-benzeneazo-γ-phenyltetronic acid. U.V. light absorption spectra in ethanol were obtained of the product crystallised from each solvent. The purple form showed maxima at $\lambda_{max} = 3360 \AA$ ($\log \varepsilon = 4.4$) and $2350 \AA$ ($\log \varepsilon = 4.2$). The yellow form (used for analysis) showed a maximum at $\lambda_{max} = 3560 \AA$ ($\log \varepsilon = 3.5$) and an inflection at $2840 \AA$ ($\log \varepsilon = 3.9$). Both spectra were unchanged by addition of hydrochloric acid.

**NITRATION**


γ-Phenyltetronic acid (5.3 g., 0.03 mol.) was ground with glacial acetic acid (15 ml.) and added to a solution of conc. nitric acid in glacial acetic acid (100 ml. of 1:9, v/v).
The mixture was heated at 30° for 0.5 hour, when solution was complete, and allowed to stand at room temperature for 48 hours. It was then poured into water (100 ml.) and chloroform extraction was carried out. The chloroform layer was washed with water, dried (Na₂SO₄) and distilled at reduced pressure, leaving a yellow oil (3.4 g., 52%) with negative nitrite test. This oil was extracted and crystallised with light petroleum (b. 60 – 80°) to give needles of α-nitro-γ-phenyltetronic acid, m.p. 110°. (Found: C, 54.60; H, 3.32; N, 5.02. C₁₀H₉O₂N requires: C, 54.29; H, 3.19; N, 6.33%). U.V. light absorption spectra were obtained and showed one maximum at 2500 A (log ε 3.8). (Gf. γ-phenyltetronic acid λ max, 2520 A, log ε 4.2).

**BROMINATION**

α-Bromo-γ-phenyltetronic acid and α,α-dibromo-γ-phenyl-β-oxobutyrolactone (Gf. Wolff and Schwabe, Ann., 1896, 221, 231).

γ-Phenyltetronic acid (17.6 g., 0.1 mol.) was dissolved in dry chloroform (600 ml.), and bromine (20.0 g., 0.125 mol.) in dry chloroform (60 ml.) was added during 0.5 hour. The solution was stirred at room temperature for a further hour, and then the bulk of the chloroform was distilled off at reduced pressure. The residual solution was washed with saturated aqueous sodium bicarbonate which was acidified and extracted with chloroform. Drying and distillation of the latter chloroform extract left a yellow crystalline solid (8.3 g., 33%) which was recrystallised from ethyl acetate/light
petroleum (b. 80 - 100°) to give the \( \alpha \)-bromo-\( \chi \)-phenyltetronic acid, m.p. 165° approx. (decomposing slowly above 100°).

(Found: C, 47.41; H, 2.91. \( \text{C}_{10} \text{H}_7 \text{O}_3 \text{Br} \) requires C, 47.08; H, 2.77%). Nitrite test positive. Chromatographically pure.

Drying and distillation at reduced pressure of the original chloroform solution left a red oil (10 g.) which was recrystallised from light petroleum (b. 60 - 80°) to give the \( \alpha \alpha \)-dibromo-\( \chi \)-phenyl-\( \beta \)-oxobutyrolactone (8.4 g., 25%) m.p. 110 - 112° (decomp.). (Found: C, 36.12; H, 2.09. \( \text{C}_{10} \text{H}_6 \text{O}_3 \text{Br}_2 \) requires C, 35.96; H, 1.81%). Nitrite test negative. An estimation of bromine-content was carried out, by heating a weighed amount of the neutral product under reflux with sodium ethoxide, acidifying, adding standard silver nitrate solution (25 ml.) and back-titrating with standard thiocyanate using iron alum as indicator.

(Found: Br, 45.07%; \( \text{C}_{10} \text{H}_6 \text{O}_3 \text{Br}_2 \) requires 47.9%).

U.V. light absorption spectra were obtained for both bromo-compounds in ethanol. \( \alpha \)-Bromo-\( \chi \)-phenyltetronic acid showed two maxima, at 2540 \( \lambda \) (log \( \varepsilon \) 4.0) (cf. \( \chi \)-phenyltetronic acid \( \lambda \) max. 2520 \( \lambda \), log \( \varepsilon \) 4.2) and 3270 \( \lambda \) (log \( \varepsilon \) 2.2).

\( \alpha \alpha \)-Dibromo-\( \chi \)-phenyl-\( \beta \)-oxobutyrolactone showed one maximum at 2680 \( \lambda \) (log \( \varepsilon \) 3.6) which decreased with concentration of the solution used.
SECTION IV

THE INFRA-RED SPECTRA OF TETRONIC ACIDS

(obtained by Dr. D. M. W. Anderson
on a Hilger H-800 Double Beam I.R.
Spectrometer, using Nujol mulls or
hexachlorobutadiene smears with
NaCl or LiF prisms where appropriate).
The Infra-Red Spectra of Tetronic Acids.

The acidic tetronic acids, and their esters, are all crystalline solids and so their absorption spectra are obtained in the solid state, in Nujol or hexachlorobutadiene, or in solution. Although a detailed examination of I.R. absorption spectra is outside the scope of this thesis, there are points in the appended tables which deserve discussion, in which intensity of absorption is denoted as strong (s), medium (m) or weak (w).

In the carbonyl frequency-range the spectra of both the α-acyltetronic acids and the remainder, two quite distinct bands are visible, as well as the strong or medium bands at 1560 - 1630 cm\(^{-1}\). (C=O stretching). The α-acetyltetronic acids all show two bands at 1750 - 1770 cm\(^{-1}\) and 1660 - 1710 cm\(^{-1}\). The tetronic acids with no α-acyl groups show as a rule one band at 1700 - 1720 cm\(^{-1}\) with, in most cases, a second at rather lower frequencies.

Since the spectrum of β-N-piperidino-(-1-hydroxy)cyclohexyl acrylic acid lactone shows only one carbonyl band at 1710 cm\(^{-1}\), it seems reasonable at first that the upper carbonyl band (1750 - 1770 cm\(^{-1}\)), present only in the α-acetyltetronic acid spectra, should be allocated to the acyl carbonyl group. This frequency, is however, that expected of αβ-unsaturated γ-lactones (Grove and Willis, loc. cit. give 1750 cm\(^{-1}\)). The enol acetates of αα-diphenyl- and αβ-spirocyclohexytetronic acids show only the band at
1750 cm$^{-1}$, due presumably to the lactone carbonyl, along with the acetate band at 1800 cm$^{-1}$. The enol benzoates of $\delta$-methyl- and $\gamma$-dimethyltetronic acids have strong bands at both 1800 cm$^{-1}$ and 1738 cm$^{-1}$. It seems that the lower frequency (1710 - 1720 cm$^{-1}$) in the other spectra can be explained by H-bonding. This is indicated clearly in the spectrum of $\alpha$-methyltetronic acid which shows a strong very broad band at 1600 - 1730 cm$^{-1}$.

A similar result was noted by Duncanson (J., 1953, 1207) in a study on a more restricted range of tetronic acid derivatives and was interpreted to mean that in the solid state tetronic acids exhibit strong intermolecular H-bonding except in $\alpha$-acetyltetronic acid where the lactone carbonyl group does not take part in H-bond formation in the solid state. The acyl C=O group presumably forms an intramolecular H-bond as in I and II:

![Diagram](image)

In this respect the supposed $\alpha$-hydroxy-$\delta$-phenyltetronic acid has a spectrum similar to those of the $\alpha$-acetyltetronic acids, with two well-defined maxima at 1765 cm$^{-1}$ and 1612 cm$^{-1}$. This is presumably due to the ability of the
**α**-hydroxyl group to form an intramolecular H-bond.

I. F. Trotter *et al.* (Biochem. J.; 1948, 42, 601) found that ascorbic and hydroxytetronic acids in the solid state have absorption maxima at 1750 cm\(^{-1}\) and 1650 cm\(^{-1}\) allocated respectively to the lactone carbonyl and the C=C groups.

The hydroxyl bands are essentially in agreement with this theory. The use of even thick smears shows at most very little free OH character, and the bands have the broadness usually ascribed to H-bonding. This bonding may be one of three types: intermolecular bonding between two or more molecules, intramolecular bonding and chelation in which resonance structures are involved. The frequency of the bonded OH absorption is a direct measure of the strength of the H bond. Resonance stabilisation gives rise to a much stronger H-bond with a consequent large low-frequency shift.

The lower frequency limits at which OH absorptions of the bonded type occur are extremely difficult to define, as the absorption bands are relatively weak and extremely broad. Reid and Ruby have already stated (*J. Amer. Chem. Soc.*; 1951, 73, 1054) that their unpublished work on tetronic acids has established that the OH frequency in these compounds occurs as low as about 2500 cm\(^{-1}\), and our work supports this. Broad weak bands due to OH chelation normally occur between 2500 cm\(^{-1}\) and 3200 cm\(^{-1}\) and are seen in the spectra of α-acetyl-γ-γ-dimethyl-, α-acetyl-γ-phenyl- and α-acetyl-γ-γ-diphenyltetronic acids, respectively.
The tetronic acids without acyl groups also show little or no free-\( \text{OH} \) character. Very strong H-bonding is apparent of a kind attributable to dimersisation and resonance stabilisation, particularly in the \( \beta \)-disubstituted tetronic acids — \( \beta \)-dimethyl-, \( \beta \)-trimethyl- and \( \beta \)-spirocyclohexyltetronic acids. With single-bridge bonding (inter- or intramolecular) the shape of \( \text{OH} \) absorption bands normally remains essentially sharp, but most intramolecular hydrogen bonds are resonance stabilised.

The position of the \( \text{OH} \) band may sometimes be found, and hence the type of bonding determined, by deuteration when the \( \text{OD} \) band appears at lower frequencies. The breadth of the band is usually much reduced, and the drop in frequency is generally uniform. The method requires care, however, as exchange with the H atoms of \( \text{OH} \) groups results in the appearance of \( \text{OD} \) absorptions in the same relative position as the \( \text{OD} \). Deuteration of \( \alpha \)-methyl-, \( \alpha \)-dimethyl- and \( \alpha \)-spirocyclohexyltetronic acids was carried out readily by heating for 0.75 hour in \( \text{D}_2\text{O} \) (with a little pure ethanol added in the second case to promote solution) and allowing to crystallise. Strong absorption was obtained in the 2100 — 2200 region, probably due in part to exchange at \( \text{CH} \) groups. This indicates the \( \text{OH} \) bands to be at about 2900 cm\(^{-1}\) — the region for enolic \( \beta \)-diketonates, which have intramolecular bonding. Since steric considerations do not allow of a direct intramolecular hydrogen bond in the tetronic
acids, this OH stretching absorption of the conjugate chelation type must arise through dimerisation into a structure capable of resonance stabilisation, as occurs in 5:5-dimethyl-1:3-cyclohexanedione (Rasmussen et al., J. Amer. Chem. Soc., 1949, 71, 1068).
Table 1. Absorption Spectra of Tetronic Acids.

<table>
<thead>
<tr>
<th>System</th>
<th>1.</th>
<th>2.</th>
<th>3.</th>
<th>4.</th>
<th>5.</th>
<th>6.</th>
<th>7.</th>
<th>8.</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3902w</td>
<td>-</td>
<td>(3930w)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(3865w)</td>
<td>(3850w)</td>
<td>-</td>
<td>3851w</td>
<td>-</td>
<td>(3812w)</td>
<td>(3832w)</td>
<td>(3865w)</td>
<td>-</td>
</tr>
<tr>
<td>(3782w)</td>
<td>(3770w)</td>
<td>-</td>
<td>3782w</td>
<td>-</td>
<td>-</td>
<td>3768</td>
<td>(3800w)</td>
<td>-</td>
</tr>
<tr>
<td>(3730w)</td>
<td>-</td>
<td>-</td>
<td>3712w</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>(3742w)</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>(3690w)</td>
<td>-</td>
<td>3641w</td>
<td>-</td>
<td>3630m</td>
<td>3612w</td>
<td>(3665w)</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>(3590w)</td>
<td>(3600w)</td>
<td>3608w</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3630m</td>
<td>3435w</td>
</tr>
<tr>
<td>-</td>
<td>(3360w)</td>
<td>-</td>
<td>3367w</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3138w</td>
<td>-</td>
<td>-</td>
<td>3122w</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<p>| OH, CH | 2950m | -  | 2948m | 2950s | 2941s | 2941s | 3130- | 2980m |
| bonded |       | -  | -  | -  | -  | -  | 2850m | 2955m |
| -OH |       | -  | -  | -  | -  | -  | -  | -  |
| region | 2500 | -  | 2873m | 2870m | 2867s | -  | -  | -  |
| -      | 2730w | 2720m | -  | 2728m | -  | -  | 2742m |
| 2700m | -  | 2670m | 2675m | 2690m | 2685m | 2693m | 2708m |
| -      | 2660w | 2650m | -  | 2668m | -  | -  | -  |
| -      | -  | -  | 2542m | -  | 2542m | 2522m | 2550w | -  |</p>
<table>
<thead>
<tr>
<th>System</th>
<th>1.</th>
<th>2.</th>
<th>3.</th>
<th>4.</th>
<th>5.</th>
<th>6.</th>
<th>7.</th>
<th>8.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-</td>
<td>2470w</td>
<td>-</td>
<td>2499m</td>
<td>-</td>
<td>2472w</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2360m</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2360w</td>
<td>2350w</td>
<td>-</td>
</tr>
<tr>
<td>2337w</td>
<td>-</td>
<td>-</td>
<td>(2330m)</td>
<td>2325w</td>
<td>2320w</td>
<td>-</td>
<td>-</td>
<td>2340w</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>2170w</td>
<td>(2140w)</td>
<td>-</td>
<td>2200w</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>(2065w)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>1932w</td>
<td>-</td>
<td>1920w</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1882w</td>
<td>(1880w)</td>
<td>-</td>
<td>1881w</td>
<td>-</td>
<td>-</td>
<td>1887w</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>(1850w)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1710m</td>
<td>(1788w)</td>
<td>1720w</td>
<td>1793w</td>
<td>1720m</td>
<td>1700m</td>
<td>1720s</td>
<td>1740w</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>1693s</td>
<td>1692m</td>
<td>1683s</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>bonding</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>1679s</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>heavy</td>
</tr>
<tr>
<td></td>
<td>1647s</td>
<td>1660m</td>
<td>1640s</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1630s</td>
<td>1620w</td>
<td>-</td>
<td>1630s</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>G=G</td>
<td>1570s</td>
<td>1557s</td>
<td>1549w</td>
<td>1550m</td>
<td>1550w</td>
<td>1595m</td>
<td>1598s</td>
<td>-1590</td>
</tr>
</tbody>
</table>
|        | -   | 1538s  | 1531w  | 1503w  | -   | -      | 1492s  | (1547w)|}
<p>|        | -   | -      | -      | 1383m  | 1467s| 1420w  | -      | -   |
|        | 1325s| -      | 1312m  | -      | 1308s| 1310w  | -      | -   |
|        | -   | 1280s  | -      | 1298m  | -   | 1282m  | 1297w  | -   |
|        | 1275s| -      | 1270m  | 1272s  | 1268m| 1257s  | 1250m  | -   |
|        | -   | 1236m  | 1243m  | 1240m  | 1242w| 1230s  | -      | -   |
|        | -   | -      | 1206m  | 1206m  | 1206w| 1217s  | 1202w  | -   |
|        | -   | 1193m  | -      | -      | -   | 1193s  | -      | -   |</p>
<table>
<thead>
<tr>
<th>System</th>
<th>1.</th>
<th>2.</th>
<th>3.</th>
<th>4.</th>
<th>5.</th>
<th>6.</th>
<th>7.</th>
<th>8.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1170s</td>
<td>-</td>
<td>1182m</td>
<td>1159m</td>
<td>1173m</td>
<td>1168m</td>
<td>1160m</td>
<td>1171w</td>
<td>-</td>
</tr>
<tr>
<td>1120m</td>
<td>-</td>
<td>-</td>
<td>1159m</td>
<td>1152m</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>1112m</td>
<td>-</td>
<td>1138m</td>
<td>1110m</td>
<td>-</td>
<td>-</td>
<td>1113m</td>
</tr>
<tr>
<td>1072m</td>
<td>-</td>
<td>-</td>
<td>1090m</td>
<td>-</td>
<td>-</td>
<td>1097w</td>
<td>1089m</td>
<td>1101m</td>
</tr>
<tr>
<td>1052m</td>
<td>(1040w)</td>
<td>1040w</td>
<td>1031w</td>
<td>1037m</td>
<td>1037w</td>
<td>1042m</td>
<td>1038m</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>(1018w)</td>
<td>-</td>
<td>-</td>
<td>1010m</td>
<td>1015m</td>
<td>1013s</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>962s</td>
<td>-</td>
<td>985s</td>
<td>970m</td>
<td>982m</td>
<td>980s</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>936m</td>
<td>-</td>
<td>940m</td>
<td>937s</td>
<td>-</td>
<td>943s</td>
<td>-</td>
</tr>
<tr>
<td>908s</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>917m</td>
<td>911s</td>
<td>924w</td>
<td>920m</td>
<td>918m</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>(863w)</td>
<td>-</td>
<td>877 s</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>810s</td>
<td>800s</td>
<td>800w</td>
<td>810m</td>
<td>820s</td>
<td>812w</td>
<td>816m</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>780m</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>771m</td>
<td>760m</td>
<td>770w</td>
<td>771m</td>
<td>-</td>
<td>773w</td>
<td>769m</td>
<td>760s</td>
<td>-</td>
</tr>
<tr>
<td>750w</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>753s</td>
<td>-</td>
<td>71s</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>720w</td>
<td>722w</td>
<td>723s</td>
<td>730s</td>
<td>723w</td>
<td>729m</td>
<td>-</td>
</tr>
<tr>
<td>703m</td>
<td>692m</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>700w</td>
<td>700s</td>
<td>-</td>
</tr>
<tr>
<td>616m</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
**α-Acyltetronic Acids and Esters.**

1. α-Acetyl-γ,δ-dimethyltetronic acid.
2. α-Benzyol-γ,δ-dimethyltetronic acid.
3. α-Acetyl-γ-phenyltetronic acid.
4. α-Acetyl-γ,δ-diphenyltetronic acid.
5. α-Hydroxy-γ-phenyltetronic acid.
6. β-N-piperidino-(1-hydroxycyclohexyl)acrylic acid lactone.
7. γ-Spirocyclohexyltetronic acid enol acetate.
8. γ,γ'-Diphenyltetronic acid enol acetate.
9. γ,γ'-Dimethyltetronic acid enol benzoate.
10. γ-Methyltetronic acid enol benzoate.

<table>
<thead>
<tr>
<th>System</th>
<th>1.</th>
<th>2.</th>
<th>3.</th>
<th>4.</th>
<th>5.</th>
<th>6.</th>
<th>7.</th>
<th>8.</th>
<th>9.</th>
<th>10.</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>(3866w)</td>
<td>(3870w)</td>
<td>(3850w)</td>
<td>-</td>
<td>(3880w)</td>
<td>(3885w)</td>
<td>(3850w)</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>(3796w)</td>
<td>(3780w)</td>
<td>(3765w)</td>
<td>-</td>
<td>(3760w)</td>
<td>(3770w)</td>
<td>(3770w)</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>(3737w)</td>
<td>(3720w)</td>
<td>(3710w)</td>
<td>-</td>
<td>(3690w)</td>
<td>(3705w)</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>(3603w)</td>
<td>(3620w)</td>
<td>(3610w)</td>
<td>-</td>
<td>(3600w)</td>
<td>(3595w)</td>
<td>(3600w)</td>
</tr>
<tr>
<td>-</td>
<td>31400w</td>
<td>-</td>
<td>-</td>
<td>(3552w)</td>
<td>(3540w)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>(3380w)</td>
<td>-</td>
<td>-</td>
<td>(3452w)</td>
<td>(3450w)</td>
<td>3420w</td>
<td>-</td>
<td>(3390w)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>(3300w)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3350w</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>(3243w)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>(3350w)</td>
</tr>
<tr>
<td>-</td>
<td>3175w</td>
<td>3170w</td>
<td>(3166w)</td>
<td>3190m</td>
<td>(broad)</td>
<td>-</td>
<td>-</td>
<td>3160w</td>
<td>(3170w)</td>
<td>-</td>
</tr>
<tr>
<td>3010w</td>
<td>3070m</td>
<td>3077m</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2982m</td>
<td>3055m</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>System</td>
<td>1.</td>
<td>2.</td>
<td>3.</td>
<td>4.</td>
<td>5.</td>
<td>6.</td>
<td>7.</td>
<td>8.</td>
<td>9.</td>
<td>10.</td>
</tr>
<tr>
<td>--------</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>-----</td>
</tr>
<tr>
<td>lactone C=O</td>
<td>1768m</td>
<td>1770w</td>
<td>1750s</td>
<td>1765w</td>
<td>1765s</td>
<td>-</td>
<td>1798m</td>
<td>1805m</td>
<td>1800s</td>
<td>1792s</td>
</tr>
<tr>
<td></td>
<td>(1715w)</td>
<td>-</td>
<td>-</td>
<td>1737w</td>
<td>-</td>
<td>-</td>
<td>1748s</td>
<td>1760s</td>
<td>1769w</td>
<td>1738s</td>
</tr>
<tr>
<td>C=O stretching</td>
<td>1692m</td>
<td>-</td>
<td>-</td>
<td>1700s</td>
<td>1710m</td>
<td>1710s</td>
<td>-</td>
<td>(1711w)</td>
<td>1696s</td>
<td>1700s</td>
</tr>
<tr>
<td>stretch</td>
<td>1660m</td>
<td>1680m</td>
<td>1660s</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>(1660w)</td>
<td>-</td>
<td>-</td>
<td>(1664w)</td>
</tr>
<tr>
<td>-C=O-</td>
<td>162.2m</td>
<td>1592m</td>
<td>1600s</td>
<td>1616s</td>
<td>1612m</td>
<td>1586s</td>
<td>1630s</td>
<td>1630s</td>
<td>1631w</td>
<td>(1635w)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1600w</td>
<td>-</td>
<td>1620w</td>
<td>-</td>
</tr>
<tr>
<td>System</td>
<td>1.</td>
<td>2.</td>
<td>3.</td>
<td>4.</td>
<td>5.</td>
<td>6.</td>
<td>7.</td>
<td>8.</td>
<td>9.</td>
<td>10.</td>
</tr>
<tr>
<td>--------</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>1556m</td>
<td>1500m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
</tr>
<tr>
<td></td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
</tr>
<tr>
<td></td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
</tr>
<tr>
<td></td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
</tr>
<tr>
<td></td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
</tr>
<tr>
<td></td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
</tr>
<tr>
<td></td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
</tr>
<tr>
<td></td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
</tr>
<tr>
<td></td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
</tr>
<tr>
<td></td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
</tr>
<tr>
<td></td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
</tr>
<tr>
<td></td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
</tr>
<tr>
<td></td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
</tr>
<tr>
<td></td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
</tr>
<tr>
<td></td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
</tr>
<tr>
<td></td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
</tr>
<tr>
<td></td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
</tr>
<tr>
<td></td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
</tr>
<tr>
<td></td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
</tr>
<tr>
<td></td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
</tr>
<tr>
<td></td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
</tr>
<tr>
<td></td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
</tr>
<tr>
<td></td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
<td>1394m</td>
</tr>
<tr>
<td>System</td>
<td>1.</td>
<td>2.</td>
<td>3.</td>
<td>4.</td>
<td>5.</td>
<td>6.</td>
<td>7.</td>
<td>8.</td>
<td>9.</td>
<td>10.</td>
</tr>
<tr>
<td>--------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>968m</td>
<td>970w</td>
<td>993s</td>
<td>980m</td>
<td>-</td>
<td>973s</td>
<td>977m</td>
<td>-</td>
<td>999s</td>
<td>999s</td>
<td>999s</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>961m</td>
<td>944m</td>
<td>-</td>
<td>940m</td>
<td>954m</td>
<td>-</td>
<td>947w</td>
<td>938m</td>
<td>938m</td>
</tr>
<tr>
<td>923m</td>
<td>939m</td>
<td>922m</td>
<td>928w</td>
<td>926w</td>
<td>-</td>
<td>928w</td>
<td>933m</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>920</td>
<td>920m</td>
<td>920w</td>
<td>-</td>
<td>910m</td>
<td>913w</td>
<td>920m</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>895m</td>
<td>-</td>
<td>893m</td>
<td>898m</td>
<td>880w</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>870m</td>
<td>-</td>
<td>862m</td>
<td>860w</td>
<td>853m</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>858w</td>
<td>848w</td>
<td>857m</td>
<td>857m</td>
<td>860w</td>
<td>850m</td>
<td>840m</td>
<td>836m</td>
<td>842m</td>
<td>858w</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>822w</td>
<td>-</td>
<td>833m</td>
<td>830w</td>
<td>815w</td>
<td>-</td>
<td>828m</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>800w</td>
<td>810w</td>
<td>792w</td>
<td>793w</td>
<td>800m</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>802w</td>
<td>-</td>
<td>(806w)</td>
</tr>
<tr>
<td>750w</td>
<td>782w</td>
<td>780m</td>
<td>783w</td>
<td>776w</td>
<td>775m</td>
<td>-</td>
<td>772m</td>
<td>778m</td>
<td>780m</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>750m</td>
<td>763m</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>755m</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>723w</td>
<td>725w</td>
<td>-</td>
<td>723w</td>
<td>-</td>
<td>727m</td>
<td>716m</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>688w</td>
<td>700m</td>
<td>697m</td>
<td>703m</td>
<td>710w</td>
<td>-</td>
<td>692s</td>
<td>699m</td>
<td>699s</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>662w</td>
<td>-</td>
<td>-</td>
<td>674m</td>
</tr>
</tbody>
</table>
AUTHOR'S ACKNOWLEDGMENTS.

I am grateful to Professor E. L. Hirst for his helpfulness, and to Dr. L. J. Haynes for his guidance and constant aid and encouragement during the course of this work. I am indebted also to Dr. D. M. W. Anderson for obtaining Infra-Red absorption spectra, and to the members already named of the Final Honours Class for help with some experimental work.

Finally, I thank the Distillers' Company, Ltd., for a grant, and the University for the award of the Hope Prize Scholarship, which allowed the work to be carried out.