Derivatives of Acetoacetic Acid. Part IV. A New Route to α-Acetyltetronic Acids.†*

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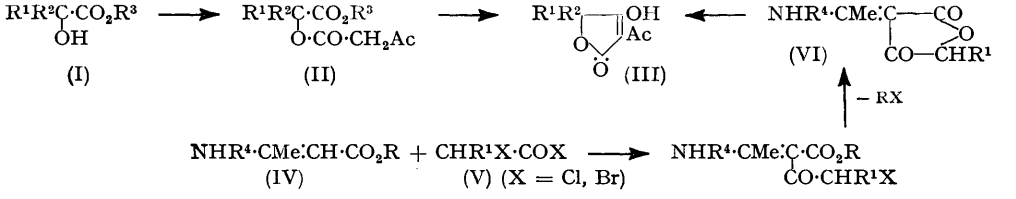
Substituted α-acetyltetronic acids were readily prepared by the Dieckmann-type cyclisation of the acetoacetates of α-hydroxy-esters: almost quantitative yields were obtained by the cyclisation of the acetoacetates of *tert.*-α-hydroxy-esters with sodium alkoxide in an alcoholic medium. Bromination of α-acetyltetronic acids in aqueous acetic acid gave α-bromotetronic acids, which could be catalytically reduced to the corresponding tetronic acids. α-Acetyltetronic acids reacted with ammonia and primary amines to give the α-aminoethylidene derivatives.

As part of the study of acetoacetates of alcohols possessing a second reactive grouping, the self-condensation was attempted of the acetoacetates of α-hydroxy-esters by a Dieckmann type of cyclisation of the alkoxycarbonyl group on to the reactive methylene group of the acetoacetic acid residue, which might be expected to provide a new route to α-acetyltetronic acids (III).

The acetoacetate of ethyl lactate was cyclised by use of sodium in toluene, facilities for the removal of lower-boiling products being provided in order to avoid alcoholysis of the



acetoacetate with the alcohol eliminated in the course of the reaction. The α-acetyl-γ-methyltetronic acid (III; R^1 = Me, R^2 = H), m. p. 54—55°, was obtained in 50% yield.

* Part III, preceding paper.

† Patents pending: B.P. Appln. 110/1951, 4251/1952, and 18779/1952.

Other experimental conditions afforded lower yields: sodium in methanol–benzene gave a 20% yield, sodium in *tert.*-butanol a 30% yield, and potassium in *tert.*-butanol a 46% yield.

The only previously described method for the synthesis of α-acetyltetronic acids, that due to Benary (*Ber.*, 1909, **42**, 3912; cf. also Baker, Grice, and Jensen, *J.*, 1943, 241; Lecocq, *Compt. rend.*, 1946, **222**, 183), involves the reaction of a β-aminocrotonate (IV) with an α-halogeno-acid halide (V) in the presence of pyridine, followed by cyclisation to (VI) and, finally, alkaline hydrolysis to (III). Baker *et al.* (*loc. cit.*) record an overall yield of 34% of α-acetyltetronic acid by this route.

Methyl mandelate reacted smoothly with diketen to give a quantitative yield of the acetoacetate (II; R^1 = Ph, R^2 = H, R^3 = Me), m. p. 56°; cyclisation by means of sodium in toluene gave α-acetyl-γ-phenyltetronic acid, m. p. 104—105°, in 55% yield.

γγ-Disubstituted α-acetyltetronic acids were also readily made by this new method. The acetoacetate of methyl α-hydroxy*iso*butyrate with sodium in toluene gave a 67% yield of α-acetyl-γγ-dimethyltetronic acid; use of sodium ethoxide in toluene–ethanol increased the yield to 92%. Methyl α-hydroxy*iso*butyrate was therefore allowed to react with methyl acetoacetate in the presence of alcoholic sodium ethoxide, it being hoped that alcoholysis would give rise to the acetoacetate (II), which would then be rapidly converted into the α-acetyltetronic acid. However, only unchanged materials were isolated. On the other hand, in a similar experiment with ethyl lactate and methyl acetoacetate in alcoholic sodium ethoxide, a small yield (10%) of α-acetyl-γ-methyltetronic acid was obtained.

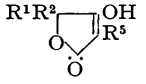
$$\underset{\text{(I)}}{R^1R^2C(OH)CO_2R^3} + CH_2Ac\cdot CO_2R \rightleftharpoons \underset{\text{(II)}}{R^1R^2C(O\cdot CO\cdot CH_2Ac)CO_2R^3} + ROH$$

An explanation of these results may be found by consideration of the alcoholysis equilibrium shown above. Acetoacetic esters undergo alcoholysis, even in the absence of catalyst, with great ease (Bader, Cummings, and Vogel, *J. Amer. Chem. Soc.*, 1951, **73**, 4195; Bader and Vogel, *ibid.*, 1952, **74**, 3992). Further, esters of *tert.*-alcohols undergo alkaline hydrolysis at a far lower rate than do those of *sec.*-alcohols (the rates for the hydrolysis of *iso*propyl acetate and *tert.*-butyl acetate, as quoted by Hammett, "Physical Organic Chemistry," McGraw-Hill, 1940, p. 211, are in the ratio 17·3 : 1), and, since the mechanisms are known to be similar, it is to be expected that similar considerations must hold for alcoholysis reactions. Thus, in an alcoholic medium, rapid alcoholysis of (II) to (I) will ensue if (II) is an ester of a *sec.*-alcohol, and, the cyclisation to α-acetyltetronic acid, being a slower reaction, only a poor yield of (III) will be obtained; although if the reaction medium is itself a *tert.*-alcohol the alcoholysis will be slower and a higher yield of acetyltetronic acid afforded. However, starting with an acetoacetate of a *tert.*-α-hydroxy-ester, the alcoholysis reaction will be much slower, permitting a high yield of α-acetyltetronic acid, while the slow alcoholysis reaction will effectively prevent the formation of α-acetyltetronic acid from a *tert.*-α-hydroxy-ester but permit a small yield from a *sec.*-α-hydroxy-ester.

In other experiments, high yields of α-acetyltetronic acids were obtained by cyclisation of acetoacetates of *tert.*-α-hydroxy-esters in alcoholic media; it is probable that purely mechanical factors (insoluble sodium salts) caused the lower yields obtained by use of sodium in benzene or toluene. Cyclisation of the acetoacetate of methyl benzilate by sodium ethoxide in ethanol–benzene gave α-acetyl-γγ-diphenyltetronic acid (III; R^1 = R^2 = Ph) in 88·5% yield; the acetoacetate of methyl 1-hydroxy*cyclo*hexanecarboxylate similarly gave a 95% yield of the α-acetyltetronic acid (III; R^1R^2 = $[CH_2]_5$>) and the use of sodium *n*-butoxide in *n*-butanol gave an almost quantitative yield. The generality of the new route was illustrated by the cyclisation of the acetoacetate (II; R^1 = R^3 = Me, R^2 = CH_2Ph) into α-acetyl-γ-benzyl-γ-methyltetronic acid again in good yield.

Attempts to extend this reaction to β-hydroxy-esters were unsuccessful. While ethyl β-hydroxybutyrate readily afforded an acetoacetate, attempted cyclisation of that ester with sodium in toluene gave only crotonic and dehydroacetic acids as recognisable products. Methyl salicylate, which might be expected to afford 3-acetyl-4-hydroxycoumarin, failed

to react with diketen in the presence of either acidic or basic catalysts, presumably as a result of steric hindrance.



(VII; R^1 = Me, R^2 = H, R^5 = CO·$[CH_2]_2$·CH_2·OH)
(VIII; R^1 = Me, R^2 = H, R^5 = CO·CHBr·CH_2·CH_2·OH)
(IX; R^1 = Me, R^2 = H, R^5 = CO·CH_2Br)
(X; R^1 = Me, R^2 = H, R^5 = Br)
(XI; R^1 = R^2 = Me, R^5 = Br)
(XII; R^1 = R^2 = Me, R^5 = H)
(XIII; R^1R^2 = $[CH_2]_5$>, R^5 = Br)
(XIV; R^1R^2 = $[CH_2]_5$>, R^5 = H)

The behaviour of α-acyltetronic acids on bromination has previously been studied by Clutterbuck, Raistrick, and Reuter (*Biochem. J.*, 1935, **29**, 300); it was shown that (+)-carolic acid (VII; shown as its hydrated form), on treatment with one mol. of bromine in acetic acid, gave (+)-monobromocarolic acid (VIII), and, that further bromination in aqueous acetic acid resulted in the removal of the side-chain and the formation of (+)-α-bromo-γ-methyltetronic acid (X).

α-Acetyl-γ-methyltetronic acid behaved analogously, giving α-bromoacetyl-γ-methyltetronic acid (XI) and α-bromo-γ-methyltetronic acid, the latter the (±)-form of that obtained from carolic acid by Clutterbuck *et al.* (*loc. cit.*). Similarly, α-acetyl-γγ-dimethyltetronic acid and α-acetyl-γ-*spirocyclo*hexanetetronic acid with two mols. of bromine in aqueous acetic acid gave α-bromo-γγ-dimethyltetronic acid (XI) and α-bromo-γ-*spirocyclo*hexanetetronic acid (XIII), respectively. Catalytic reduction of the α-bromotetronic acids (Clutterbuck *et al., loc. cit.*; Reuter and Welch, *J. Proc. Roy. Soc. N.S. Wales*, 1939, **72**, 120) gave the known γγ-dimethyltetronic acid (XII) and γ-*spirocyclo*hexanetetronic acid (XIV).

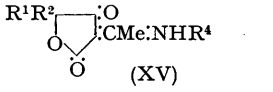
The α-acetyltetronic acids readily formed ketonic derivatives which, as has been shown for α-acetyltetronic acid itself by Benary (*Ber.*, 1910, **43**, 1065), involve the side-chain carbonyl group. Thus, the phenylhydrazones and semicarbazones are soluble in sodium hydrogen carbonate solution and colour ferric chloride solutions red, indicating a formula (XVI), where R^4 = NHPh or NH·CO·NH_2. Benary had found that acetyl chloride and α-acetyltetronic acid phenylhydrazone gave a pyrazolone. However, we found that this reagent with the phenylhydrazones of α-acetyl-γ-methyltetronic acid and of the γ-phenyl analogue gave the *O*-acetyl derivatives. In contrast, the α-acetyltetronic acids themselves are unaffected by acetyl chloride (cf. Clutterbuck *et al., loc. cit.*), recalling the non-reactivity of the hydroxy-group in analogous derivatives of 3-acetyl-4-hydroxycoumarin (Heilbron and Hill, *J.*, 1927, 1705). This behaviour is possibly attributable to hydrogen-bonding of the hydroxyl group with the acetyl group.

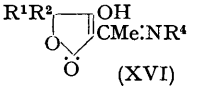
Wide differences were exhibited by α-acetyltetronic acids on hydrolysis. While a small yield of γ-methyltetronic acid was obtained by alkaline hydrolysis of α-acetyl-γ-methyltetronic acid, similar treatment of the γ-phenyl and γγ-dimethyl analogues resulted in extensive break-down. On the other hand, the γ-*spirocyclo*hexane- and γ-benzyl-γ-methyl derivatives were substantially unaffected by boiling 10% sodium hydroxide, and the former resisted even boiling concentrated hydrochloric acid and 80% sulphuric acid at 100°. Only with α-acetyl-γγ-diphenyltetronic acid were good results obtained, a 61% yield of γγ-diphenyltetronic acid being obtained by hydrolysis with cold aqueous alkali.

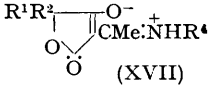
Benary (*Ber.*, 1909, **42**, 3918) found that heating of α-acetyltetronic acid with aniline gave (VI; R^1 = H, R^4 = Ph) that had previously been obtained as an intermediate in his synthesis. This is a general reaction of α-acetyltetronic acids which readily afford "amides" with ammonia and primary amines: secondary amines, however, gave salts. Benary has suggested that since the "amides" are neutral compounds affording no colour with ferric chloride, but are soluble in sodium hydroxide solution (this we have confirmed only in certain cases), they possess the structure (XV), but readily rearrange to the ketimine (XVI) with alkali. Light-absorption determination (see Table) give clear evidence in favour of structure (XV), since the "amides" derived from ammonia and aliphatic amines exhibit strong absorption bands at 2250—2310 Å and 2830—2940 Å. The latter band is incompatible with the ketimine structure (XVI), but is to be expected for the system N·C:C·C:O possessed by (XV), the shift to higher wave-lengths arising from the

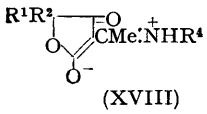
auxochromic effect of the amino-substituent (Bowden, Braude, Jones, and Weedon, *J.*, **1946**, 45; Bowden, Braude, and Jones, *ibid.*, p. 948). The bands exhibited by the α-acetyltetronic acid amides at 2250—2310 Å, which are considerably more intense than the absorption exhibited in this region by the aminocrotonic esters, may be attributable to interaction of the carbonyl and carboxyl groups in the dipolar resonance forms (XVII and XVIII).

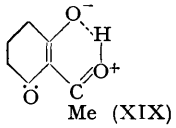
α-Acetyltetronic acids exhibit two absorption bands at 2300—2360 and at 2600—2680 Å (cf. Herbert and Hirst, *Biochem. J.*, 1935, **29**, 1881). Similar behaviour has been

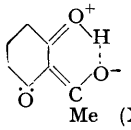

(XV)


(XVI)


(XVII)


(XVIII)


Me (XIX)


Me (XX)

noted in the case of enolised β-triketones (Birch and Todd, *J.*, 1952, 3102), and Smith (*J.*, 1953, 803) has ascribed the bands exhibited by 2-acetyl*cyclo*hexane-1 : 3-dione at 2350 and 2750 Å (in methanol), respectively, to the αβ-unsaturated carbonyl group and the conjugated diene chromophore in a ring formed by an intramolecular hydrogen bond, as in (XIX) and (XX). Comparison (see Table) of the spectra of α-acetyltetronic acids

Light-absorption data (in ethanolic solution).

α-Acetyltetronic acids.

	$\lambda_{max.}$, Å	$\varepsilon_{max.}$	$\lambda_{max.}$, Å	$\varepsilon_{max.}$
(III; $R^1 = R^2 = H$) [1]	2300	15,000	2650	15,000
(III; R^1 = Me, R^2 = H)	2300	9,100	2600	12,000
(III; $R^1 = R^2$ = Me)	2300	9,500	2640	13,800
(III; R^1 = Ph, R^2 = H)	2360	12,000	2670	15,150
(III; $R^1 = R^2$ = Ph)	2300	10,050	2680	17,000
(III; $R^1R^2 = [CH_2]_5>$)	2300	10,050	2660	14,500
(III; $R^1 = CH_2Ph$, R^2 = H)	2300	9,800	2650	16,000
γγ-Dimethyltetronic acid (XII) [2]	2230	13,500	—	—
HO·CMe:CHAc [3]	2690	12,000	—	—

[1] Herbert and Hirst, *loc. cit.*, determined in water. [2] Jones and Whiting, *J.*, 1949, 1419. [3] Grossmann, *Z. physikal. Chem.*, 1924, **109**, 305, determined in hexane.

Enamines.

	$\lambda_{max.}$, Å	$\varepsilon_{max.}$	$\lambda_{max.}$, Å	$\varepsilon_{max.}$
(XVI; $R^1 = R^2$ = Me, R^3 = H)	2250	8,700	2830	20,000
(XVI; $R^1R^2 = [CH_2]_5>$, R^3 = Me)	2290	11,000	2910	27,700
(XVI; $R^1 = R^2$ = Ph, R^3 = Me)	2310	11,500	2940	25,000
(XVI; R^1 = Ph, R^2 = H, R^3 = Ph)	2300	11,600	3050	23,000
Et_2N·CMe:CH·CO_2Et [1]	2850	30,500	2880	30,500
NHPh·CMe:CH·CO_2Et [2]	2940	11,500	—	—

[1] Bowden, Braude, Jones, and Weedon, *loc. cit.* [2] Jones and Whiting, *J.*, 1949, 1423.

with those of γγ-dimethyltetronic acid and acetylacetone shows that the bands at 2300—2360 Å are to be associated with interaction between the enol double bond and the carboxyl group, and that the bands at 2600—2680 Å can be attributed to the HO·C:C·CO·CH_3 chromophore. Exaltation of the absorption band observed in the latter case must be due partly to the auxochromic effect of the HO substituent but chiefly to the increased resonance arising from intramolecular hydrogen bonding.

Calam, Todd, and Waring (*Biochem. J.*, 1949, **45**, 520) found that anhydrotetronic acid possessed appreciable activity in causing the hatching of the potato-root eelworm (*Heterodera rostochiensis*), although it was much less active than the naturally secreted agent. The following α-acetyltetronic acids were tested by Dr. D. W. Fenwick of the Nematology Department, Rothamstead Experimental Station: III; R^1 = Me, R^2 = H; R^1 = Ph,

$R^2 = H$; $R^1 = R^2 = Me$; $R^1 = R^2 = Ph$. Dr. Fenwick concluded that none of the four compounds was capable of stimulating larval emergence in *Heterodera rostochiensis* under *in vitro* conditions.

Experimental

M. p.s were determined on a Kofler block and are corrected.

Acetoacetate of Ethyl Lactate (II; $R^1 = Me$, $R^2 = H$, $R^3 = Et$).—To an agitated mixture of ethyl lactate (59 g.) and triethylamine (0·5 c.c.) at 65—75° diketen (42 g.) was added during 1 hr., and the product was then heated for a further ½ hr. Distillation gave the *ester* (89·3 g., 89%), b. p. 132—136°/14 mm., n_D^{20} 1·4350 (Found: C, 53·5; H, 7·15. $C_9H_{14}O_5$ requires C, 53·45; H, 7·0%).

α-Acetyl-γ-methyltetronic Acid (III; $R^1 = Me$, $R^2 = H$).—Sodium (11·5 g.) was rapidly added to an agitated mixture of the above ester (101 g.) and toluene (150 c.c.), which was then gently heated under a short fractionating column with a total reflux still-head; a vigorous reaction ensued with deposition of solid sodium salts. Gentle heating was continued for 1 hr. during which material, b. p. 70—90° (20 c.c.), was removed from the still-head. Next morning, aqueous hydrochloric acid (50 c.c. of acid and 50 c.c. of water) was added with cooling. Thorough extraction with ether, followed by distillation, afforded the tetronic acid (39·5 g., 50%), b. p. 120—126°/15 mm., m. p. 54—55° [from ether–light petroleum (b. p. 60—80°)] (Lecocq, *loc. cit.*, gives m. p. 55°) (Found: C, 53·9; H, 5·1. Calc. for $C_7H_8O_4$: C, 53·85; H, 5·15%). Cyclisation of the acetoacetate (50·5 g.) by refluxing it for 2 hr. with sodium *tert.*-butoxide (from 5·75 g. of sodium and 150 c.c. of *tert.*-butanol) gave a 30%, and the use of potassium *tert.*-butoxide (from 9·8 g. of potassium and 150 c.c. of *tert.*-butanol) a 46% yield.

The reaction of α-acetyl-γ-methyltetronic acid (1·5 g.) with phenylhydrazine (1 g.) in boiling benzene (10 c.c.) for 10 min., followed by addition of light petroleum and cooling, gave the *phenylhydrazone* (2·0 g.), m. p. 165° [from ethyl acetate–light petroleum (b. p. 60—80°)] (Found: C, 63·35; H, 5·6; N, 11·3. $C_{13}H_{14}O_3N_2$ requires C, 63·4; H, 5·75; N, 11·4%). When the phenylhydrazone (4·5 g.) was refluxed in chloroform (30 c.c.) with acetyl chloride (3 g.) for 3 hr., there was obtained the *acetyl* derivative (3·8 g.), m. p. 175° [from ethyl acetate–light petroleum (b. p. 40—60°)] (Found: C, 62·0; H, 5·45; N, 9·95. $C_{15}H_{16}O_4N_2$ requires C, 62·5; H, 5·6; N, 9·7%).

α-Acetyl-γ-methyltetronic acid (5 g.), methanol (10 c.c.), and ammonia solution (*d* 0·88; 5 c.c.) were refluxed for 1 hr., and then concentrated. The amide (XV; $R^1 = Me$, $R^2 = R^4 = H$) (1·9 g.) crystallised from *n*-butanol as needles, m. p. 159—160° (Lecocq, *loc. cit.*, gives m. p. 161°) (Found: C, 54·4; H, 5·75. Calc. for $C_7H_9O_3N$: C, 54·2; H, 5·85%).

Acetoacetate of Methyl Mandelate (II; $R^1 = Ph$, $R^2 = H$, $R^3 = Me$).—Methyl mandelate was prepared from mandelic acid and methanol by Clinton and Laskowski's method (*J. Amer. Chem. Soc.*, 1948, **70**, 3135) in 88% yield. Diketen (89 g.) was added dropwise during 0·5 hr. to an agitated, boiling mixture of methyl mandelate (166 g.), benzene (200 c.c.), and triethylamine (1 c.c.) which was then refluxed for a further 0·5 hr. Removal of the solvent and crystallisation of the residue (250 g.) from benzene–light petroleum (b. p. 40—60°) gave the *acetoacetate* as needles, m. p. 56° (Found: C, 62·3; H, 5·4. $C_{13}H_{14}O_5$ requires C, 62·4; H 5·65%).

α-Acetyl-γ-phenyltetronic Acid (III; $R^1 = Ph$, $R^2 = H$).—To a warm agitated solution of the above ester (200 g.) in toluene (200 c.c.) small pieces of sodium (19 g.) were added. The vigorous initial reaction was moderated by external cooling, after which the mixture was refluxed for 3·5 hr., material (50 c.c.), b. p. 55—80°, being distilled off meanwhile. The product was acidified with concentrated hydrochloric acid (80 c.c.)–water (100 c.c.) and then extracted with benzene. Removal of the solvent and crystallisation of the residue (95 g., 54·5%) from ethyl acetate–light petroleum (b. p. 60—80°) gave the tetronic acid as pale yellow needles, m. p. 104—105° (Lecocq, *loc. cit.*, gives m. p. 104°) (Found: C, 65·85; H, 4·35. Calc. for $C_{12}H_{10}O_4$: C, 66·05; H, 4·6%).

The acid (2 g.) and phenylhydrazine (1·1 g.) in methanol gave the *phenylhydrazone*, which crystallised from methanol in needles, m. p. 157—158° (Found: N, 8·95. $C_{18}H_{16}O_3N_2$ requires N, 9·1%). The phenylhydrazone (1 g.) was heated with acetyl chloride (2 c.c.) in chloroform (20 c.c.) for 1 hr.; removal of solvents, trituration of the gummy residue with methanol, and crystallisation of the solid (0·8 g.) from chloroform-light petroleum (b. p. 60—80°) gave the *acetyl* derivative as needles, m. p. 197° (Found: N, 8·05. $C_{20}H_{18}O_4N_2$ requires N, 8·0%).

α-Acetyl-γ-phenyltetronic acid (1 g.), aniline (0·5 g.), and ethanol (10 c.c.) were refluxed for

5 min., part of the ethanol was then removed, and water was added. Crystallisation of the deposit from aqueous ethanol gave the *anilide* (XV; $R^1 = R^4 = Ph$, $R^2 = H$) as needles, m. p. 117° (Found: C, 73·7; H, 5·2; N, 4·5. $C_{18}H_{15}O_3N$ requires C, 73·7; H, 5·15; N, 4·8%).

Acetoacetate of Methyl α-Hydroxyisobutyrate (II; $R^1 = R^2 = R^3 = Me$).—Diketen (75 g.) was added during 0·5 hr. to methyl α-hydroxy*iso*butyrate (100 g.) and triethylamine (0·5 c.c.) at 60—70°, and the mixture heated at 70° for a further 0·5 hr. The product when distilled gave the *acetoacetate* (151 g., 88%), b. p. 118—125°/12 mm., n_D^{20} 1·4400 (Found: C, 53·6; H, 7·45. $C_9H_{14}O_5$ requires C, 53·45; H, 7·0%).

α-Acetyl-γγ-dimethyltetronic Acid (III; $R^1 = R^2 = Me$).—(*a*) Sodium (11·5 g.), in small pieces, was added to a warm, agitated solution of the above acetoacetate (101 g.) in toluene (150 c.c.). The reaction proceeded as previously described, and during isolation, a solid (57 g., 67%), m. p. 52—58°, was obtained on washing with cold light petroleum. Crystallisation from ether–light petroleum (b. p. 40—60°) gave the *tetronic acid* as pale yellow needles, m. p. 64—65°, b. p. 108—110°/12 mm. (Found: C, 56·45; H, 6·0. $C_8H_{10}O_4$ requires C, 56·45; H, 5·9%).

(*b*) A solution of the acetoacetate (46 g.) in toluene (25 c.c.) was added to one of sodium ethoxide (from 5·5 g. of sodium and 100 c.c. of ethanol), which was then refluxed for 4 hr. and set aside overnight. Most of the solvents were removed, and ether and concentrated hydrochloric acid (25 c.c.)–water (25 c.c.) were added. The solid residue (37 g., 98%), obtained with ether, was washed with light petroleum and then gave an almost pure product (35·5 g.), m. p. 58—59°. The *phenylhydrazone* crystallised from aqueous ethanol as prisms, m. p. 157·5—158° (Found: C, 64·95; H, 5·9; N, 10·5. $C_{14}H_{16}O_3N_2$ requires C, 64·6; H, 6·2; N, 10·75%).

The tetronic acid (1 g.) was warmed with ammonia solution (*d* 0·88; 2 c.c.) at 60° for 1 hr. and then set aside. The precipitated *amide* (XV; $R^1 = R^2 = Me$, $R^4 = H$), on crystallisation from water, gave needles, m. p. 181—182° (Found: C, 56·6; H, 6·65; N, 8·65. $C_8H_{11}O_3N$ requires C, 56·8; H, 6·55; N, 8·3%).

Acetoacetate of Methyl Benzilate (II; $R^1 = R^2 = Ph$, $R^3 = Me$).—Benzilic acid was esterified with methanol by Clinton and Laskowski's method (*loc. cit.*). To the ester (170 g.) in boiling benzene (200 c.c.) containing triethylamine (1 c.c.), diketen (61 g.) was added, with agitation, during 1 hr. After a further hour's refluxing, the solvent was removed and the residue (228 g.) crystallised twice from methanol, yielding the *acetoacetate* as needles, m. p. 91—92° (Found: C, 69·75; H, 5·45. $C_{19}H_{18}O_5$ requires C, 69·95; H, 5·55%).

α-Acetyl-γγ-diphenyltetronic Acid (III; $R^1 = R^2 = Ph$).—A mixture of sodium ethoxide solution (from 4·6 g. of sodium and 70 c.c. of ethanol) and the above acetoacetate (62 g.) in benzene (100 c.c.) was refluxed for 3 hr., set aside overnight, and then worked up as previously described. The product (52 g.; m. p. 90—95°) was washed with ether–light petroleum (b. p. 40—60°) and crystallised from *n*-butanol, giving the *tetronic acid* as a pale yellow solid, m. p. 102° (Found: C, 73·15; H, 5·0. $C_{18}H_{14}O_4$ requires C, 73·45; H, 4·8%). The phenylhydrazone was an oil, but a *semicarbazone* was obtained as needles, m. p. 186—188°, from ethyl acetate (Found: N, 11·9. $C_{19}H_{17}O_4N_3$ requires N, 11·95%).

The tetronic acid (1·47 g.) in ethanol (3 c.c.) was warmed with aqueous methylamine (40%; 1 c.c.). Addition of water gave a solid (1·2 g.) which, on recrystallisation from aqueous ethanol, gave the *amide* (XV; $R^1 = R^2 = Ph$, $R^4 = Me$) as needles, m. p. 182—183° (Found: C, 73·9; H, 5·25; N, 4·55. $C_{19}H_{17}O_3N$ requires C, 74·25; H, 5·55; N, 4·55%).

Acetoacetate of Methyl 1-Hydroxycyclohexanecarboxylate (II; $R^1R^2 = [CH_2]_5>$, $R^3 = Me$).—1-Hydroxy*cyclo*hexanecarboxylic acid was esterified by Clinton and Laskowski's method (*loc. cit.*). The methyl ester (118 g.), b. p. 68—72°/0·5 mm., n_D^{20} 1·4612, in boiling benzene (100 c.c.) and triethylamine (0·5 c.c.), was treated with diketen (65 g.) as previously described. The *acetoacetate* had b. p. 130—132°/1 mm., n_D^{20} 1·4683 (Found: C, 60·0; H, 7·5. $C_{12}H_{18}O_5$ requires C, 59·5; H, 7·5%).

α-Acetyl-γ-spirocyclohexanetetronic Acid (III; $R^1R^2 = [CH_2]_5>$).—The acetoacetate (74·5 g.) in benzene (100 c.c.) was added to sodium methoxide solution (from 7·0 g. of sodium and 100 c.c. of methanol), and the mixture refluxed for 4 hr. and set aside overnight. The product was concentrated, acidified, and extracted as previously described but with chloroform. Evaporation of the solvents and crystallisation of the yellow solid (63 g.), m. p. 108—115°, from methanol gave the *tetronic acid* (60 g., 95%) as white needles, m. p. 125—126° (Found: C, 62·85; H, 6·7. $C_{11}H_{14}O_4$ requires C, 62·75; H, 6·7%). The 2:4-*dinitrophenylhydrazone* crystallised in yellow needles, m. p. 195—196°, from ethanol (Found: C, 52·5; H, 4·75; N, 14·0. $C_{17}H_{18}O_7N_4$ requires C, 52·3; H, 4·65; N, 14·35%).

When a solution of the tetronic acid (1 g.) in aqueous methylamine (20%; 4 c.c.) was warmed, an oil was deposited which slowly crystallised. Recrystallisation from aqueous

methanol gave the *amide* (XV; $R^1R^2 = [CH_2]_5>$, R^4 = Me) as needles, m. p. 126° (Found: C, 64·3; H, 7·4; N, 6·55. $C_{12}H_{17}O_3N$ requires C, 64·55; H, 7·7; N, 6·3%).

The reaction of the tetronic acid (2·1 g.) in hot methanol (10 c.c.) with diethylamine (1 c.c.) afforded the *diethylamine* salt as needles, m. p. 180—181°, from ethanol (Found: C, 63·7; H, 8·95; N, 4·7. $C_{15}H_{25}O_4N$ requires C, 63·6; H, 8·9; N, 4·95%). The salt dissolved in water, and an immediate precipitate of the tetronic acid was obtained on addition of dilute hydrochloric acid.

Acetoacetate of Methyl 2-Hydroxy-1-phenylpropane-1-carboxylate (II; R^1 = CH_2Ph, R^2 = R^3 = Me).—*Methyl 2-hydroxy-1-phenylpropane-2-carboxylate* (I; R^1 = CH_2Ph, R^2 = R^3 = Me) was prepared from the acid in 58% yield; it had b. p. 84—87°/3 mm., n_D^{20} 1·5080 (Found: C, 68·45; H, 7·3. $C_{11}H_{14}O_3$ requires C, 68·05; H, 7·1%). Diketen (19·5 g.) was added to a refluxing solution of the ester (42·2 g.) in benzene (100 c.c.) containing triethylamine (0·5 c.c.). The *acetoacetate* was obtained as a pale yellow oil (43·7 g., 72·5%), b. p. 144—150°/1·5 mm., n_D^{20} 1·5047 (Found: C, 65·0; H, 6·5. $C_{15}H_{18}O_5$ requires C, 64·75; H, 6·5%).

α-Acetyl-γ-benzyl-γ-methyltetronic Acid (III; R^1 = CH_2Ph, R^2 = Me).—The acetoacetate (40·7 g.) in benzene (50 c.c.) was refluxed with sodium ethoxide solution (from 3·5 g. of sodium and 50 c.c. of ethanol) for 4 hr. After acidification of the solution and isolation of the product with ether, an oil was obtained that crystallised when rubbed with light petroleum. Crystallisation of the solid (30 g., 89%) from aqueous methanol gave the *tetronic acid* as pale yellow needles, m. p. 92—93° (Found: C, 68·45; H, 5·9. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·75%).

A solution of the acid (1 g.) in methanol (10 c.c.) was refluxed with *p*-toluidine (0·6 g.) for 0·5 hr. Addition of water and cooling precipitated the *toluidide* (XV; R^1 = $PhCH_2$, R^2 = Me, R^3 = *p*-Me·C_6H_4), which formed needles (from aqueous methanol), m. p. 143° (Found: C, 75·3; H, 6·25; N, 4·2. $C_{21}H_{21}O_3N$ requires C, 75·2; H, 6·3; N, 4·2%).

Bromination of α-Acetyltetronic Acids.—[Unless otherwise stated these bromo-compounds were crystallised from ethyl acetate–light petroleum (b. p. 60—80°).] (a) *α-Bromoacetyl-γ-methyltetronic acid* (IX). To a solution of α-acetyl-γ-methyltetronic acid (1·56 g.) in acetic acid (5 c.c.) at 40° a solution of bromine in acetic acid (1M; 10 c.c.) was added during 1 hr. Evaporation *in vacuo* and washing with ether–light petroleum (b. p. 40—60°) gave a solid (1·4 g., 60%), from which the *bromo*-compound (IX) was obtained as pale yellow needles, m. p. 135° (decomp.) (Found: C, 36·0; H, 3·3; Br, 33·7. $C_7H_7O_4Br$ requires C, 35·8; H, 3·0; Br, 34·0%).

(b) *α-Bromo-γ-methyltetronic acid* (X). After the addition of 1 mol. of bromine as described above, water (10 c.c.) and more bromine solution (1M; 10 c.c.) at 20° were added. Evaporation as above at 30° and crystallisation gave (±)-α-bromo-γ-methyltetronic acid (1·0 g., 52%) as prisms, m. p. 172° [Raistrick *et al.*, *loc. cit.*, give m. p. 172° for (+)-α-bromo-γ-methyltetronic acid].

(c) *α-Bromo-γγ-dimethyltetronic acid* (XI). Bromine in acetic acid (1M; 10 c.c.) was added dropwise during 0·5 hr. to a solution of α-acetyl-γγ-dimethyltetronic acid (1·7 g.) in acetic acid (5 c.c.) at 30°. Water (10 c.c.) was added followed by more bromine solution (1M; 10 c.c.) at 20°. The resulting solution was evaporated *in vacuo*, and the product (1·7 g.), m. p. 173—178°, crystallised, giving the *bromo-tetronic acid* as prisms, m. p. 186—187°, soluble in sodium hydrogen carbonate solution and giving a red colour with ferric chloride solution (Found: C, 34·95; H, 3·2; Br, 38·5. $C_6H_7O_3Br$ requires C, 34·8; H, 3·4; Br, 38·6%). A solution of the bromo-tetronic acid (2·07 g.) in methanol (10 c.c.) and barium hydroxide solution (0·2N; 50 c.c.) was agitated with palladium–charcoal (0·2 g.; 3% Pd) in an atmosphere of hydrogen (uptake: 254 c.c. at 21°/771 mm. in 30 min. Theory 238 c.c.). After filtration and evaporation of the solution, the solid residue was extracted with ethyl acetate to give γγ-dimethyltetronic acid (XII), which crystallised from ethyl acetate–light petroleum (b. p. 60—80°) as prismatic needles (0·9 g.), m. p. 142—143° (Benary, *Ber.*, 1907, **40**, 1082, gives m. p. 142—143°).

(d) *α-Bromo-γ-spirocyclohexanetetronic acid* (XIII). α-Acetyl-*γ-spirocyclo*hexanetetronic acid (2·1 g.) was brominated as described in (c). Evaporation gave the *bromo-tetronic acid* (3·7 g.) which crystallised from ethyl acetate as prisms, m. p. 216—217°, soluble in sodium hydrogen carbonate solution and giving a red colour with ferric chloride solution (Found: C, 43·95; H, 4·3; Br, 32·3. $C_9H_{11}O_3Br$ requires C, 43·75; H, 4·5; Br, 32·35%). Hydrogenation of the bromo-tetronic acid (2·47 g.), as described in (c), resulted in the absorption of 240 c.c. of gas at 20°/770 mm. (theory, 237 c.c.) in 50 min. Isolation as above afforded *γ-spirocyclo*hexanetetronic acid (XIV) (1·2 g.) as prisms, m. p. 198—199°, from ethyl acetate (Jones and Whiting, *J.*, 1949, 1421, give m. p. 198°).

Hydrolysis of α-Acetyltetronic Acids.—(a) *α-Acetyl-γ-methyltetronic acid.* The acid (5 g.) was dissolved in aqueous sodium hydroxide (3 g. in 5 c.c.) with cooling and, after 1 hr. at room

temperature, the solution was heated at 50° for 3 hr. After acidification and isolation with ether, an oil was obtained which crystallised when rubbed with aqueous methanol and was recrystallised from the same solvent. γ-Methyltetronic acid (0·15 g.) formed needles, m. p. 116—117° (Benary, *Ber.*, 1911, **44**, 1763, gives m. p. 117—119°).

(b) *α-Acetyl-γγ-diphenyltetronic acid.* A solution of the acid (2·94 g.) in sodium hydroxide solution (5%; 16 c.c.) was set aside at room temperature for 6 hr.: after 2 hr., deposition of solid commenced. Acidification afforded a yellow solid (2·0 g.) which, after two crystallisations from aqueous methanol, gave γγ-diphenyltetronic acid (1·6 g.) as pale yellow needles, m. p. 213° (Lecocq, *Compt. rend.*, 1946, **222**, 299, gives m. p. 212°) (Found: C, 76·0; H, 4·75. Calc. for $C_{16}H_{12}O_3$: C, 76·15; H, 4·8%).

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