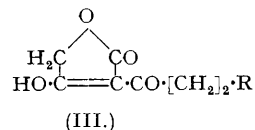
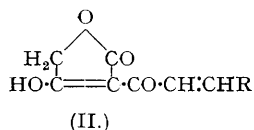
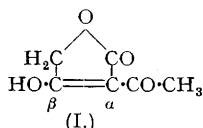


62. Synthesis of Some α -Acyltetronic Acids.

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α -Acetyltetronic acid (I) is readily synthesised from β -anilincrotonic ester and chloroacetyl chloride. The methyl group of (I) is reactive and condenses with benzaldehyde, anisaldehyde, cinnamaldehyde and furfuraldehyde to give unsaturated compounds of the type (II), which have been reduced to the saturated α -acyltetronic acids (III). The furfurylidene derivative is reduced simultaneously to the tetrahydrofuran compound. The oxime of α -acetyltetronic acid is convertible into α -acetamidotetronic acid.

DERIVATIVES of α -acyltetronic acids are frequently found as products of mould metabolism, and the synthesis of such compounds is, therefore, of some interest. The only successful method previously described is due to Benary (*Ber.*, 1909, **42**, 3912), who condensed chloroacetyl chloride with ethyl β -aminocrotonate in pyridine, cyclised the resulting α -chloroacetyl- β -aminocrotonic ester with loss of ethyl chloride by heating to give " α -acetyltetronamide," and deaminated this by alkaline hydrolysis, thus obtaining α -acetyltetronic acid (I). The yield was not stated. Benary also describes the preparation by similar methods of α -acetyltetronanilide, but did not hydrolyse it to (I).



The preparation of α -acetyltetronanilide has been considerably simplified, and it is now shown that it is readily hydrolysed in cold alkaline solution to α -acetyltetronic acid (I), which may be directly extracted from the acidified solution. The overall yield of (I) from molecular quantities of methyl or ethyl acetoacetate and chloroacetyl chloride is 34%.

The methyl group of α -acetyltetronic acid is, as expected, less reactive than that in a simple methyl ketone. All tetronic acids are very powerful acids, the anion being stabilised by a resonance distribution of the charge between the oxygen atoms of the acidic hydroxyl group and of the ester carbonyl group (see Kumler, *J. Amer. Chem. Soc.*, 1938, **60**, 859) (the α -carbon atom is also involved to a certain extent, since its chemical behaviour resembles that of an *o*-carbon atom in a phenol). In α -acetyltetronic acid the charge is also distributed on the oxygen atom of the α -carbonyl group, thus making it an even stronger acid, but at the same time the methyl group shows diminished reactivity owing to its partial ionic character, $:\text{C}(\text{O}^-)\cdot\text{CH}_3$. In confirmation it has been found that both α -acetyl- and α -carbethoxy-tetronic acids are appreciably stronger acids than tetronic acid, the pK values being for tetronic acid, 3.76 (Kumler, *loc. cit.*), α -acetyl- and α -carbethoxy-tetronic acids approximately 1.8. We wish to express our thanks to Dr. E. P. Abraham of the Sir William Dunn School of Pathology, Oxford, for the determination of the last two values.

Aldehydes do not condense with the methyl group of (I) in alkaline solution but react in glacial acetic acid solution in presence of a little piperidine to give poor yields of condensation products which are not easily isolated. In this way (I) has been condensed with benzaldehyde, cinnamaldehyde, furfuraldehyde and anisaldehyde to give the unsaturated derivatives (II; R = Ph, Ph \cdot CH:CH, C₄H₉O, and *p*-MeO \cdot C₆H₄), α -(β -phenylacrylyl)-, α -(β -styrylacrylyl)-, α -(β -furylacrylyl)-, and α -(*p*-methoxyphenylacrylyl)-tetronic acids respectively. Catalytic reduction of the first three of these substances yielded the saturated α -acyltetronic acids (III; R = Ph, Ph \cdot CH₂ \cdot CH₂, and C₄H₉O), α -(β -phenylpropionyl)-, α -(δ -phenylvaleryl)-, and α -(β -2-tetrahydrofurylpropionyl)-tetronic acids; in the case of the furfurylidene derivative the furan nucleus was also reduced.

The oxime of α -acetyltetronic acid undergoes the Beckmann transformation when treated with phosphorus pentachloride in phosphorus trichloride, and is converted into α -acetamidotetronic acid.

EXPERIMENTAL.

α -Acetyltetronic Acid (I).—(1) *Methyl β -aminocrotonate.* A mixture of methyl acetoacetate (150 g. or ethyl acetoacetate, 168 g.), aniline (120 g.), and a drop of concentrated hydrochloric acid as catalyst (see Coffey, Thompson, and Wilson, J., 1936, 856) was kept overnight, the separated water distilled off under diminished pressure on the water-bath, and the last traces of water removed by similar distillation after the addition of benzene (100 c.c.). The oily residue solidified completely on seeding in the case of the methyl ester. (2) *Anilide of α -acetyltetronic acid.* To the preceding product, dissolved in dry ether (400 c.c.) and anhydrous pyridine (102 g.; 1 mol.), was added during 1 hour chloroacetyl chloride (145 g.; 1 mol.) in dry ether (150 c.c.) whilst cooling in ice and shaking; after 1½ hours the ether was removed on the water-bath. Methyl or ethyl chloride was slowly evolved from the residue when heated on the water-bath for 1½ hours and then in an oil-bath for 4 hours while the temperature was slowly raised from 120° to 130°. To the light brown solid, water (1 l.) was added; after heating, the mass was powdered, collected, washed well with water, and dried on the steam-bath (yield, 164 g.). This crude anilide was refluxed for 1 hour with alcohol (500 c.c.), cooled, collected, washed twice with alcohol (200 c.c. each time) and dried (yield, 121 g.; m. p. 180—184°; lit. m. p. 188—189°). (3) *α -Acetyltetronic acid.* A mixture of the anilide (121 g.) and a solution of sodium hydroxide (30 g.) in water (450 c.c.) was shaken for 24 hours, filtered after shaking with ether (150 c.c.), and the aqueous layer again extracted with ether (75 c.c.). After acidification with concentrated hydrochloric acid (120 c.c.) and addition of salt (150 g.) the solution was extracted 16 times with chloroform (75 c.c. each time); the extracts after drying over sodium sulphate were distilled (the last few c.c. of chloroform were removed in a current of air while warm), leaving α -acetyltetronic acid (67 g.; m. p. 78—80°). By crystallisation in portions from light petroleum (b. p. 80—100°) the pure, colourless product was obtained (yield, 63 g.; m. p. 81—82°; lit. m. p. 79.5—80.5°).

α -(β -Phenylacrylyl)tetronic Acid (II; R = Ph).— α -Acetyltetronic acid (7.1 g.), benzaldehyde (5.3 g.; 1 mol.), glacial acetic acid (25 c.c.), and piperidine (1 c.c.) were heated on the water-bath for 2½ hours, and stirred into water (200 c.c.). The dark red product was collected, dried, dissolved in chloroform (150 c.c.), and shaken in portions with 0.5% aqueous sodium hydroxide (500 c.c. in all). The aqueous layer was filtered and acidified at 40°, giving a yellow, amorphous product (2.4 g.), which was crystallised first from methyl alcohol (65 c.c.; charcoal), and then from light petroleum (650 c.c.; b. p. 80—100°), being obtained in yellow or light brown needles (1 g.), m. p. 138—140° (Found in material again crystallised from light petroleum: C, 67.8; H, 4.4. $C_{13}H_{10}O_4$ requires C, 67.8; H, 4.4%). In dilute alcoholic solution it gives an orange ferric chloride reaction, and its solutions in alkali are colourless.

α -(β -Phenylpropionyl)tetronic Acid (III; R = Ph).—The preceding acid (0.75 g.) in *N*-sodium hydroxide (4 c.c.) and ethyl alcohol (10 c.c.) was shaken in hydrogen in presence of Raney nickel. Reduction, which was at first rapid, almost ceased after the uptake of hydrogen corresponding to 1 molecule. The liquid was filtered and acidified; the solid thus obtained crystallised from light petroleum (b. p. 80—100°) in colourless, flat prisms (0.54 g.), m. p. 131° after softening at 128° (Found: C, 67.0; H, 5.2. $C_{13}H_{12}O_4$ requires C, 67.2; H, 5.2%). It is slightly soluble in water and the solution gives an orange precipitate with ferric chloride. Hydrolysis with 2*N*-sulphuric acid for 4 hours gave, after removal of acetol by distillation of the neutralised solution, a 50% yield of β -phenylpropionic acid. The distillate was treated with a solution of 2:4-dinitrophenylhydrazine in hydrochloric acid; the bis-2:4-dinitrophenylhydrazone of methylglyoxal, which very slowly separated, formed orange-red crystals from nitrobenzene-toluene, m. p. 300° (lit., m. p. 300°).

*α -(β -*p*-Methoxyphenylacrylyl)tetronic Acid (II; R = *p*-MeO·C₆H₄).*—The condensation of α -acetyltetronic acid with anisaldehyde was effected as in the case of benzaldehyde. The diluted reaction mixture was extracted with warm ethyl acetate, and the organic layer shaken with *N*-sodium hydroxide, from which the crude condensation product was precipitated with hydrochloric acid. Crystallisation from 50% alcohol (charcoal) and then light petroleum (b. p. 80—100°) gave bright yellow needles (2% yield), m. p. 164° after softening at 159° (Found: C, 64.5; H, 4.7. $C_{14}H_{12}O_5$ requires C, 64.6; H, 4.7%). Its colourless sodium salt is sparingly soluble in water.

α -(β -Styrylacrylyl)tetronic Acid (II; R = Ph·CH₂·CH).— α -Acetyltetronic acid was condensed with cinnamaldehyde as in the case of benzaldehyde. After cooling, the product was collected, washed with acetic acid and then alcohol, dissolved in a large volume of warm *N*/20-sodium hydroxide (charcoal), filtered, precipitated with hydrochloric acid, collected, and crystallised from a mixture of equal volumes of acetic acid and alcohol, being obtained in orange-yellow spherulitic growths of minute needles (21% yield), m. p. 178—182° (Found: C, 70.1; H, 4.8. $C_{15}H_{12}O_4$ requires C, 70.3; H, 4.7%). Its solutions in alkalis are almost colourless.

α -(δ -Phenylvaleryl)tetronic Acid (III; R = Ph·CH₂·CH₂).—The preceding acid (1 g.) in *N*-sodium hydroxide and alcohol (25 c.c.) was shaken in hydrogen in presence of Raney nickel, rather less than 2 mols. of hydrogen being absorbed. The product obtained by acidification of the filtrate was dissolved in boiling water (220 c.c.), filtered, and concentrated hydrochloric acid (3 c.c.) added; the product which separated from the cooled solution crystallised from light petroleum (b. p. 60—80°) in very pale yellow, flat needles (0.33 g.), m. p. 81.5—82.5° (Found: C, 68.8; H, 6.2. $C_{15}H_{14}O_4$ requires C, 69.2; H, 6.2%). The acid is slightly soluble in water and is thrown out on the addition of mineral acid. The aqueous solution gives an orange precipitate with ferric chloride.

α -(β -2-Furylacrylyl)tetronic Acid (II; R = C₄H₃O).— α -Acetyltetronic acid (7 g.) was condensed, as in the previous cases, with furfuraldehyde (1 mol.). The mixture was heated for 2 hours and stirred into water (400 c.c.), and the product collected, washed, dissolved in benzene (50 c.c.), and extracted into dilute sodium hydroxide solution. After treatment with ether and charcoal, the alkaline solution was acidified, and the product collected, washed, dried (3.6 g.), and crystallised from light petroleum (b. p. 80—100°), giving orange-yellow, microcrystalline spherulitic growths, m. p. 146—148° (Found: C, 59.9; H, 3.7. $C_{11}H_8O_5$ requires C, 60.0; H, 3.6%). Solutions of the substance in alkali are almost colourless.

α -(β -2-Tetrahydrofurylpropionyl)tetronic Acid (III; R = C₄H₇O).—The above acid (1 g.) in *N*-sodium hydroxide (20 c.c.) and Raney nickel was shaken in hydrogen for 20 hours. Absorption of hydrogen was smooth and ceased after 3 mols. had been taken up. The filtered solution was acidified, filtered, and extracted continuously with ether for 8 hours; the extracts gave a solid product, which separated from light petroleum (b. p. 60—80°) in colourless flakes (0.3 g.), m. p. 73.5—74° (Found: C, 58.6; H, 6.1. $C_{11}H_{14}O_5$ requires C, 58.4; H, 6.2%). The substance gives an orange colour with aqueous ferric chloride.

α -Acetamidotetronic Acid [With Miss E. J. MACNAIR].—To α -acetyltetronic acid oxime (7.5 g.; Benary, *Ber.*, 1910, 43, 1068), dissolved in phosphorus trichloride (25 g.), was slowly added phosphorus pentachloride (4.2 g.) with cooling in ice. After ½ hour at room temperature the phosphorus trichloride was removed in the cold under diminished pressure, and the dark product added to ice; the pale yellow crystals which separated from the solution on cooling were collected, washed, and crystallised twice from alcohol. A further amount of material was obtained by repeated extraction of the aqueous solution with ether. The total yield of the pure product, which crystallised in small needles, m. p. 170°, was 2.1 g. (Found: C, 46.0; H, 4.4; N, 8.7. $C_8H_7O_4N$ requires C, 45.9; H, 4.5; N, 8.8%).