792. *Tetronic Acids and Related Compounds. Part I. Synthesis from α-Hydroxy-esters.**

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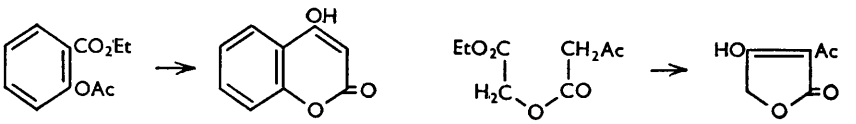
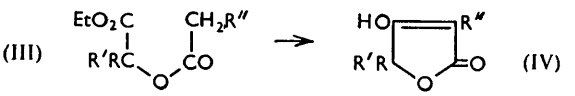
Cyclisation of α-acetoxy- and α-phenylacetoxy-esters by an internal Claisen ester reaction is investigated as a route to the synthesis of tetronic acids. The reaction proceeds very satisfactorily with esters of hydroxy-esters in which the hydroxyl group is tertiary when di*iso*propylamino-magnesium bromide is used as the condensing agent.

Several methods for the preparation of tetronic acids have been described: all depend on preparation of a γ-hydroxy-, γ-acetoxy-, or γ-halogeno-β-keto-ester and subsequent closure of the lactone ring. One standard route for the preparation of 4-hydroxycoumarin (I), which is formally related to a tetronic acid, is cyclisation of ethyl *o*-acetoxybenzoate by treatment with sodium,[1] an internal Claisen ester condensation taking place. Surprisingly, however, this type of reaction in which the O·CO of the lactone ring is not involved in the cyclisation, has received no attention as a route to tetronic acids save for a recent paper by Lacey [2] which described the cyclisation of acetoacetic esters derived by the action of diketen on α-hydroxy-esters to give acetyltetronic acids, *e.g.*, (II). An interest in tetronic acids led us to examine the internal Claisen condensation of the simple esters of α-hydroxy-esters.



(I) (II)



In our first attempt, ethyl acetoxyacetate (III; R = R′ = R″ = H) was treated with metallic sodium without solvent: there was little if any reaction at room temperature, but vigorous reaction at about 120°. The sodium dissolved completely, a brown solid (presumably a sodio-derivative) separated, and ethyl acetate appeared to be formed. However, cautious treatment of the solid with mineral acid gave no material giving a positive ferric chloride reaction and no tetronic acid could be isolated. Similar results were obtained with ethyl α-acetoxypropionate. We therefore turned to phenylacetates

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[1] (*a*) Pauly and Lockemann, *Ber.*, 1915, **48**, 28; (*b*) Stahmann, Wolff, and Link, *J. Amer. Chem. Soc.*, 1943, **65**, 2285.

[2] Lacey, *J.*, 1954, 832.

of α-hydroxy-esters in the hope that the activation of the methylene group by the adjacent phenyl group would facilitate the cyclisation.

Treatment of ethyl (phenylacetoxy)acetate (III; R = R′ = H, R″ = Ph) in xylene with sodium at 140° resulted in a *ca.* 20% yield of α-phenyltetronic acid (IV; R = R′ = H, R″ = Ph). Similarly ethyl α-(phenylacetoxy)propionate (III; R = Me, R′ = H, R″ = Ph) gave γ-methyl-α-phenyltetronic acid (IV; R = Me, R′ = H, R″ = Ph) in 24% yield, and ethyl α-phenyl-α-(phenylacetoxy)acetate (III; R = H, R′ = R″ = Ph) gave αγ-diphenyltetronic acid (IV; R = H, R′ = R″ = Ph) in 34% yield. Ethyl phenylacetoxysuccinate (III; R = CH_2·CO_2Et, R′ = H, R″ = Ph) under these conditions gave no identifiable products apart from phenylacetic acid. The ester (III; R = Me, R′ = H, R″ = CO_2Et) from ethoxycarbonylacetyl chloride and ethyl lactate gave a small quantity of γ-methyltetronic acid: presumably the initial product, α-ethoxycarbonyl-γ-methyltetronic acid (IV; R = Me, R′ = H, R″ = CO_2Et), underwent hydrolysis and decarboxylation during the isolation or during the reaction.

We then turned our attention to the reagent used to effect the cyclisation. The use of di*iso*propylaminomagnesium bromide to effect Claisen ester condensations was first described by Frostick and Hauser,[3] and recently Royals and Turpin [4] have found that this reagent is very effective in promoting mixed ester condensations. It also proved more suitable than sodium for our purpose. Ethyl α-(phenylacetoxy)propionate gave a 60% yield of γ-methyl-α-phenyltetronic acid, and ethyl α-(phenylacetoxy)phenylacetate gave a 58% yield of αγ-diphenyltetronic acid, although ethyl (phenylacetoxy)acetate gave only a 21% yield of α-phenyltetronic acid. Still better yields were obtained in the cyclisations of phenylacetates of hydroxy-esters in which the hydroxyl group was tertiary: thus ethyl α-methyl-α-(phenylacetoxy)propionate (III; R = R′ = Me, R″ = Ph) gave a 65% yield of γγ-dimethyl-α-phenyltetronic acid (IV; R = R′ = Me, R″ = Ph). Moreover, cyclisation of the acetyl derivatives of hydroxy-esters of this type proceeds satisfactorily: ethyl α-acetoxy-α-methylpropionate (III; R = R′ = Me, R″ = H) gives a 46% yield of γγ-dimethyltetronic acid (IV; R = R′ = Me, R″ = H), and methyl acetoxydiphenylacetate (III; R = R′ = Ph, R″ = H) gives an 85% yield of γγ-diphenyltetronic acid (IV; R = R′ = Ph, R″ = H).

Surprisingly, the use of di*iso*propylaminomagnesium bromide to effect the cyclisation of methyl *o*-acetoxybenzoate to 4-hydroxycoumarin was much less effective than the use of sodium, only a 2% yield being obtained; methyl *o*-phenylacetoxybenzoate gave only 11% of 4-hydroxy-3-phenylcoumarin. The sole acidic product from ethyl phenylacetoxysuccinate with di*iso*propylaminomagnesium bromide was phenylacetic acid, and it is noteworthy that from the above cyclisation of methyl *o*-acetoxybenzoate a considerable amount of methyl salicylate was recovered together with unchanged starting material. It seems possible that ester cleavage competes with cyclisation.

Nevertheless, this internal cyclisation makes a very clean and convenient route for the preparation of some tetronic acids and we are now investigating its application to the synthesis of more complex tetronic acids.

Experimental

Ethyl α-(Ethoxycarbonylacetoxy)propionate (III; R = Me, R′ = H, R″ = CO_2Et).—Ethoxycarbonylacetyl chloride (43 g.) was added during 2 hr. to ethyl lactate (59 g.) in dry pyridine (100 c.c.) at 0°, and the mixture set aside overnight, then poured into water and extracted with ether. The ether extract was washed with aqueous sodium hydrogen carbonate, dilute sulphuric acid, and water, dried (Na_2SO_4), and evaporated. The residue gave *ethyl α-(ethoxycarbonylacetoxy)propionate* (29·6 g., 44%), b. p. 103—104°/0·1 mm., n_D^{14} 1·4310 (Found: C, 52·0; H, 6·8. $C_{10}H_{16}O_6$ requires C, 51·7; H, 6·9%).

Similarly were prepared:

Ethyl (phenylacetoxy)acetate (III; R = R′ = H, R″ = Ph) [from phenylacetyl chloride (131 g.) and ethyl glycollate (66·8 g.)] (75 g., 50%), b. p. 120°/0·05 mm., n_D^{14} 1·5017 (Found: C, 65·6; H, 6·4. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·4%).

[3] Frostick and Hauser, *J. Amer. Chem. Soc.*, 1949, **71**, 1350.
[4] Royals and Turpin, *ibid.*, 1954, **76**, 5452.

Ethyl α-(phenylacetoxy)propionate (III; R = Me, R′ = H, R″ = Ph) [from phenylacetyl chloride (100 g.) and ethyl lactate (54 g.)] (73·1 g., 67%), b. p. 110°/0·2 mm., n_D^{14} 1·4917 (lit.,[5] b. p. 161°/13 mm., n_D^{19} 1·4904).

Ethyl α-phenyl-α-(phenylacetoxy)acetate (III; R″ = R′ = Ph, R = H) [from phenylacetyl chloride (110 g.) and ethyl mandelate (100 g.)] (125 g., 75%), b. p. 164—168°/0·1 mm., n_D^{16} 1·5397 (Found: C, 72·5; H, 5·8. $C_{18}H_{18}O_4$ requires C, 72·4; H, 6·1%) (the ester did not always distil satisfactorily in bulk).

Ethyl α-methyl-α-phenylacetoxypropionate (III; R = R′ = Me, R″ = Ph) [from phenylacetyl chloride (15·4 g.) and ethyl α-hydroxy-α-methylpropionate [6] (9·9 g.)] (10 g., 56%), b. p. 150°/7 mm., n_D^{13} 1·4886 (Found: C, 67·6; H, 7·3. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·3%).

Ethyl (phenylacetoxy)succinate (III; R = $CH_2 \cdot CO_2Et$; R′ = H, R″ = Ph) [from phenylacetyl chloride (109 g.) and ethyl malate (95 g.)] (85 g., 55%), b. p. 153—160°/15 mm., n_D^{19} 1·4900 (Found: C, 62·4; H, 6·5. $C_{16}H_{20}O_6$ requires C, 62·3; H, 6·5%).

Cyclisations with Sodium.—α-Phenyltetronic acid (IV; R = R′ = H, R″ = Ph). A mixture of ethyl phenylacetoxyacetate (31·1 g.), sodium (3·0 g.), and toluene (50 g.) was heated to boiling. A brown solid separated as the sodium dissolved. The suspension was treated with hydrochloric acid, the toluene layer separated, and the aqueous layer extracted with ether and benzene. Solvents were evaporated from the combined dried (Na_2SO_4) extracts: recrystallisation of the residue from aqueous methanol gave α-phenyltetronic acid (5·0 g., 20%), m. p. 256—257° (lit.,[7] 254°) (Found: C, 68·2; H, 4·4. Calc. for $C_{10}H_8O_3$: C, 68·1; H, 4·6%).

γ-Methyl-α-phenyltetronic acid (IV; R = Me, R′ = H, R″ = Ph). A mixture of ethyl α-(phenylacetoxy)propionate (33·9 g.), sodium (3·0 g.), and toluene (45 ml.) was stirred vigorously and heated to the b. p.; reaction did not begin until the toluene was almost boiling but was then vigorous. After 15 min. the mixture was a thick brown syrup. This was treated as above, giving γ-methyl-α-phenyltetronic acid (8 g., 29%) which after drying at 100°/10 mm. for 6 hr. had m. p. 165°, resolidifying and then melting at 181—182° (lit.,[8] m. p. 178°).

αγ-Diphenyltetronic acid (IV; R = R″ = Ph, R′ = H). Ethyl α-phenyl-α-(phenylacetoxy)-acetate (15·4 g.) was treated with sodium (1·2 g.) in toluene (25 ml.) as described above. When the mixture was treated with acid, αγ-diphenyltetronic acid (4·6 g., 33%) separated. Recrystallised from aqueous ethanol it had m. p. 205—208° (lit.,[9] m. p. 209°).

γ-Methyltetronic acid (IV; R = Me, R′ = R″ = H). Ethyl α-(ethoxycarbonylacetoxy)-propionate (5·8 g.) was treated with sodium (0·6 g.) in toluene (25 ml.) as described above. The mixture was treated with hydrochloric acid (3 ml. of concentrated acid in 4 ml. of water), and the aqueous layer separated and extracted with ether. The ether extract was then extracted with aqueous sodium hydrogen carbonate, and the alkaline solution acidified with dilute sulphuric acid and extracted with ethyl acetate (continuous extraction). Evaporation of the ethyl acetate gave a dark brown oil (1·8 g.) which solidified. Recrystallisation from ethyl acetate–light petroleum (b. p. 60—80°) gave γ-methyltetronic acid, m. p. 115° (lit.,[10] m. p. 118°).

Cyclisations with Diisopropylaminomagnesium Bromide.—α-Phenyltetronic acid (IV; R = R′ = H, R″ = Ph). Ethyl (phenylacetoxy)acetate (26·0 g.) in dry ether (50 ml.) was added during 1 hr. to a stirred ethereal suspension of di*iso*propylaminomagnesium bromide [from magnesium (7·3 g.), ethyl bromide (33 g.), and then di*iso*propylamine (30·3 g.)]; a white solid separated. The mixture was stirred for a further ½ hr. with gentle warming. The orange mixture was poured on ice (200 g.) and hydrochloric acid (25 ml.). The aqueous layer was separated and extracted with ether, and the combined ether extracts were then extracted with aqueous sodium hydrogen carbonate. Acidification of the alkaline extract precipitated α-phenyltetronic acid (4·5 g., 21%), m. p. 259—261°.

γ-Methyl-α-phenyltetronic acid (IV; R = Me, R′ = H, R″ = Ph). Ethyl α-(phenylacetoxy)propionate (11·8 g.) was added during 1 hr. to an ethereal suspension of di*iso*propylaminomagnesium bromide [from magnesium (2·4 g.), ethyl bromide (10·9 g.), and di*iso*propylamine (10·1 g.)], and the mixture was refluxed ½ hr. and then kept overnight. Dilute hydrochloric acid (25 ml. of concentrated acid in 75 ml. of water) was added, and the aqueous layer separated and saturated with sodium chloride and extracted with ether. The combined extracts were extracted with aqueous sodium hydrogen carbonate; acidification then precipitated

[5] Kenyon, Phillips, and Turley, *J.*, 1925, **127**, 399.
[6] Hepworth, *J.*, 1919, **115**, 1203.
[7] Dimroth and Eble, *Ber.*, 1906, **39**, 3929.
[8] Dimroth and Feuchter, *Ber.*, 1903, **36**, 2255.
[9] Kohler, Petersen, and Bickel, *J. Amer. Chem. Soc.*, 1934, **56**, 2006.
[10] Benary, *Ber.*, 1911, **44**, 1759.

γ-methyl-α-phenyltetronic acid (5·9 g., 60%) which on recrystallisation from aqueous methanol had m. p. 165°, resolidifying and then melting at 180°.

αγ-Diphenyltetronic acid (R = R″ = Ph, R′ = H). Ethyl α-phenyl-α-(phenylacetoxy)-acetate (14·8 g.) and ethereal di*iso*propylaminomagnesium bromide (from magnesium, 2·4 g.) by a similar procedure gave αγ-diphenyltetronic acid (7·3 g., 58%), m. p. 205—208° after recrystallisation from ethanol.

γγ-Dimethyltetronic acid (IV; R = R′ = Me, R″ = H). This was obtained from ethyl α-acetoxy-α-methylpropionate (12·0 g.) and ethereal di*iso*propylaminomagnesium bromide (from magnesium, 2·4 g.). The final extraction of the acidified carbonate extract was with ethyl acetate by continuous extraction. γγ-Dimethyltetronic acid (4·1 g., 64%) had m. p. 140—142° (lit.,[11] m. p. 142°) after crystallisation from benzene.

γγ-Dimethyl-α-phenyltetronic acid (IV; R = R′ = Me, R″ = Ph). From ethyl α-methyl-α-(phenylacetoxy)propionate (3·7 g.) and di*iso*propylaminomagnesium bromide (from magnesium, 1·0 g.) gave this *acid* (1·95 g., 64%), m. p. 210—213° (from aqueous ethanol) (Found: C, 70·3; H, 5·9. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%).

γγ-Diphenyltetronic acid (IV; R = R′ = Ph, R″ = H). Obtained from methyl acetoxydiphenylacetate (14·2 g.) and ethereal di*iso*propylaminomagnesium bromide (from magnesium, 2·4 g.), this acid (9·2 g., 85%) had m. p. 212° (from ethanol) (lit.,[12] m. p. 212°).

4-Hydroxycoumarin. Methyl *o*-acetoxybenzoate (19·4 g.) in ether (50 ml.) was added dropwise during 1¼ hr. to ethereal di*iso*propylaminomagnesium bromide (from magnesium, 2·43 g.). A vigorous reaction occurred during the addition and a brown solid separated. Isolation through aqueous sodium hydrogen carbonate as above gave 4-hydroxycoumarin (250 mg., 1·5%), m. p. 212° (lit.,[1b] m. p. 214—216°). Ether was evaporated from the carbonate-washed solution, and the oily residue dissolved in boiling light petroleum (b. p. 80—100°), which, on cooling, deposited colourless crystals (700 mg.), m. p. *ca.* 135°, which gave a purple colour with ferric chloride but were insoluble in aqueous sodium hydrogen carbonate. This product is being examined further. The residue (16·6 g.) from the light petroleum mother-liquors contained methyl *o*-acetoxybenzoate and methyl salicylate. Repetition of this experiment using only one-third of the quantity of methyl *o*-acetoxybenzoate gave virtually the same yield of 4-hydroxycoumarin.

4-Hydroxy-3-phenylcoumarin.—Prepared from methyl *o*-phenylacetoxybenzoate[1] (12·3 g., 0·05 mol.) and ethereal di*iso*propylaminomagnesium bromide (from magnesium, 2·43 g., 0·1 mol.), 4-hydroxy-3-phenylcoumarin (1·18 g., 10·9%) had m. p. 234° (lit.,[1b] m. p. 234—235°).

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[11] Benary, *Ber.*, 1907, **40**, 1079; Jones and Whiting, *J.*, 1949, 1419.
[12] Lecocq, *Compt. rend.*, 1946, **222**, 299.