A Synthesis of Tetronic Acid [Furan-2(3*H*),4(5*H*)-dione] and Three Analogues

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A synthesis of four tetronic acids [furan-2(3*H*) 4(5*H*)-diones] is described. On treatment with triethylamine the readily prepared diethyl α-(chloroacetyl)malonate yielded ethyl 2-ethoxy-4,5-dihydro-4-oxofuran-3-carboxylate (*ca.* 50%), which was converted into tetronic acid by alkali, and into 3-ethoxycarbonyltetronic acid by water, in high yields. 5-Methyl-, 5-phenyl-, and 5-ethyl-tetronic acids were prepared analogously. The last compound was also obtained by hydrogenation of 5-ethylidenetetronic acid.

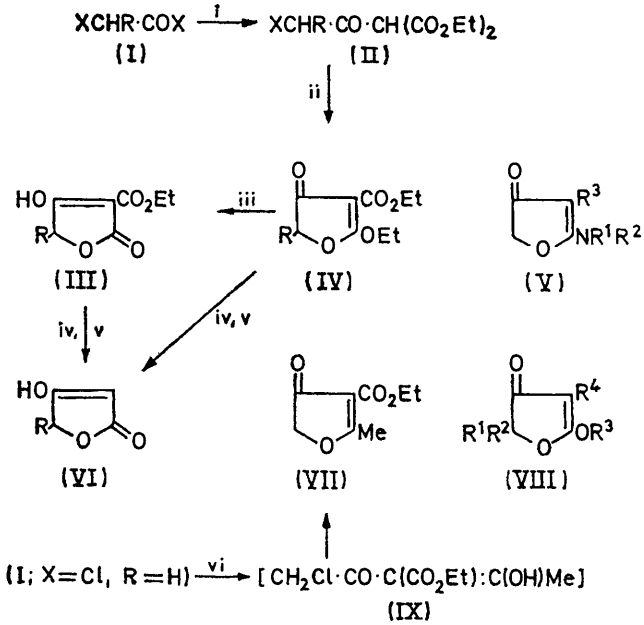
TETRONIC ACIDS have been synthesised by many routes of varying generality (see ref. 1), but available routes to tetronic acid itself (VI; R = H), appear to be mediocre. We have found that tetronic acid can be prepared relatively easily in about 40% overall yield from diethyl malonate by way of ethyl 2-ethoxy-4,5-dihydro-4-oxofuran-3-carboxylate (IV; R = H) (Scheme 1).

The most convenient available preparative method for tetronic acid is probably Benary's original route [2,3] from diethyl malonate and chloroacetyl chloride, as improved by Haynes *et al.*,[4] which yields 3-ethoxycarbonyltetronic acid (III; R = H); the ester group is then removed [5] with barium hydroxide, giving an overall yield of about 19%.

In the method of Haynes *et al.*, the reaction of chloroacetyl chloride with 1 equiv. of diethyl ethoxymagnesiomalonate gave a 60% yield of the intermediate diethyl

[1] L. J. Haynes and J. R. Plimmer, *Quart. Rev.*, 1960, **14**, 292.
[2] E. Benary, *Ber.*, 1907, **40**, 1079.
[3] E. Benary, *Ber.*, 1911, **44**, 1759.
[4] L. J. Haynes, J. R. Plimmer, and A. H. Stanners, *J. Chem. Soc.*, 1956, 4661.
[5] F. Reuter and R. B. Welch, *J. Proc. Roy. Soc. New South Wales*, 1938, **72**, 120.

chloroacetylmalonate (II; R = H, X = Cl), which was cyclised in boiling xylene. Benary's preparation, which employs 2 equiv. of diethyl sodiomalonate yielded, besides 3-ethoxycarbonyltetronic acid, a by-product, $C_9H_{12}O_5$, for which the structure originally proposed [3]



SCHEME 1 Reagents: i, EtO·Mg·CH(CO$_2$Et)$_2$; ii, Et$_3$N–PhH; iii, H$_2$O; iv, OH$^-$; v, H$^+$; vi, EtO·Mg·CH(COMe)·CO$_2$Et

was amended [6,7] to ethyl 2-ethoxy-4,5-dihydro-4-oxofuran-3-carboxylate (IV; R = H). This compound gave 3-ethoxycarbonyltetronic acid when treated with water.

that under suitable conditions, the latter compound and its analogues might give reasonable yields of the corresponding 2-ethoxydihydrofurans (IV), thus providing an alternative route to tetronic acids under mild conditions. This sequence was successful for the synthesis of tetronic acid, and 5-methyl-, 5-ethyl-, and 5-phenyltetronic acids. For tetronic acid the route is less laborious and probably gives a better yield than published methods.

Two methods of preparing the intermediate halogenoacylmalonates (II) were used (Table 1). The first, under conditions similar to those described [4] by Haynes *et al.* for (II; R = H, X = Cl) always gave over 90% yields of the latter compound and of the analogues (II; R = Et, X = Br) and (II; R = Ph, X = Cl). Conducting the reaction as described [12] for *o*-nitrobenzoyl chloride was satisfactory for α-bromopropionyl bromide, but not for chloroacetyl chloride or α-chlorophenylacetyl chloride. The products were used in crude form and were reasonable pure as judged by halogen content.

When treated with triethylamine in benzene (alcohol or ether were less satisfactory as solvents), the halogenoacylmalonates yielded the corresponding ethyl 4-oxo-4,5-dihydrofuran-3-carboxylates, which were recrystallised, generally once, before use. Compound (IV; R = H) was dimorphic; the more stable form was identical with material obtained in 13% yield from chloroacetyl chloride and diethyl sodiomalonate, essentially as described by Benary.[2] The dihydrofurans could be stored unchanged for many weeks at 0° in the absence of moisture. Samples left on the bench became yellow and oily, though the phenyl analogue (IV; R = Ph) was less soluble in water and more stable than the others. The dihydrofurans

TABLE 1

Yields (%)

(II)	Method 1	Method 2	(IV) (recrystallised)		(VI)	From (IV)	Overall
R = H, X = Cl	95	66	R = H	52	R = H	90	43
R = Me, X = Br		95	R = Me	83	R = Me	89	70
R = Et, X = Br	100		R = Et	70	R = Et	85	59
R = Ph, X = Cl	96	Impure	R = Ph	64	R = Ph	93	57

2-Alkoxyfuran-4(5*H*)-ones do not seem to have been considered as potentially useful intermediates for the synthesis of tetronic acids, although at least two, (VIII; R^1 = R^2 = H, R^3 = R^4 = Me) [1,8,9] and (VIII; R^1 = R^2 = Ph, R^3 = Et, R^4 = CO$_2$Et),[10,11] obtained respectively from the reaction of 3-methyltetronic acid with diazomethane, and that of ethyl diazoacetate with diphenylketen, are hydrolysed to the corresponding tetronic acids by water. Since the formation of Benary's by-product was presumably due to the reaction of the second equiv. of sodiomalonate with the unisolated intermediate (II; R = H, X = Cl), it seemed possible

showed strong i.r. absorption at *ca.* 1730, 1695, and 1580 cm^{-1} in chloroform, and u.v. maxima at 221—222 and 248—251 nm (Table 2).

Treatment of the 2-ethoxydihydrofurans (IV) with cold aqueous alkali gave the corresponding tetronic acids (VI) (Table 1), in high yields, and in almost pure form. Potassium hydroxide was satisfactory for the 5-methyl and 5-phenyl analogues and barium hydroxide for compounds (IV; R = H) and (IV; R = Et). Alternatively, the ethoxydihydrofurans could be hydrolysed to the 3-ethoxycarbonyltetronic acids (III) with cold water. Compound (IV; R = Ph) was sparingly

[6] R. Anschutz, *Ber.*, 1912, **45**, 2374.
[7] E. Benary, *Ber.*, 1912, **45**, 3682.
[8] F. H. Stodola, O. L. Shotwell, and L. B. Lockwood, *J. Amer. Chem. Soc.*, 1952, **74**, 5415.
[9] A. H. Stanners, Ph.D. Thesis, Edinburgh, 1956.
[10] A. S. Kende, *Chem. and Ind.*, 1956, 1053.
[11] J. W. M. Jamieson, Ph.D. Thesis, Edinburgh, 1957.
[12] G. A. Reynolds and C. R. Hauser, *Org. Synth.*, 1963, Coll. Vol. IV, p. 708.

soluble in cold water and hydrolysis was carried out in cold aqueous ethanol; hydrolysis was rapid in hot water, but gave an impure product.

Benary [2,7] obtained ethyl 2-amino-4,5-dihydro-4-oxofuran-3-carboxylate (V; $R^1 = R^2 = H$, $R^3 = CO_2Et$) and *N*-substituted analogues by treating the 2-ethoxydihydrofuran (IV; R = H) with ammonia and with

TABLE 2

U.v. data [$\lambda_{max.}$/nm (ε)]

(IV; R = H)	222 (12,500) 248 (17,800)	(III; R = H)	226 (12,700) 243 (13,300)
(IV; R = Me)	222 (11,900) 248 (19,000)	(III; R = Me)	223 (13,600) 248 (16,500)
(IV; R = Et)	221 (13,400) 248 (18,100)	(III; R = Et)	223 (13,000) 249 (16,500)
(IV; R = Ph)	221 (18,600) 251 (14,700)	(III; R = Ph)	218 (13,500) 250 (14,500)
(VII)	212 (9330) 259 (11,500)		

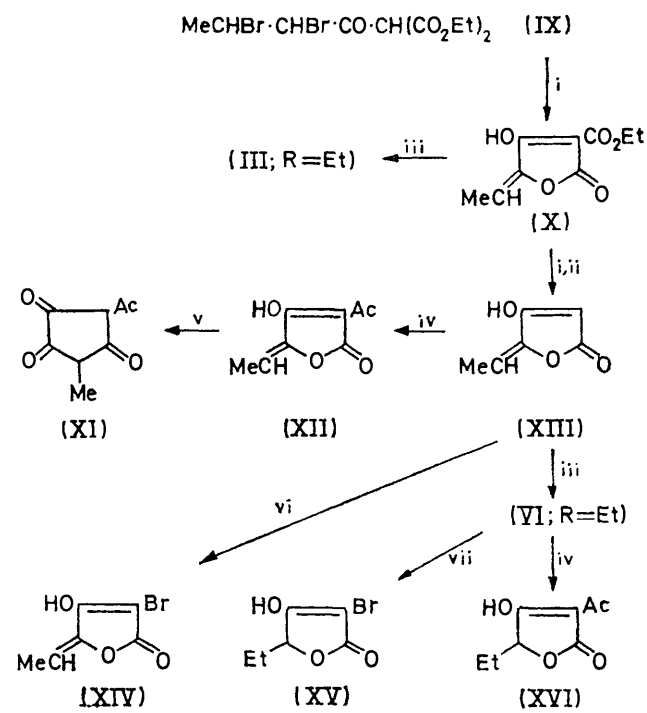
amines. These and similar derivatives are conveniently prepared directly from diethyl chloroacetylmalonate by successive treatments with triethylamine and with ammonia or with a primary or secondary amine, without isolating the intermediate 2-ethoxydihydrofuran.

The products were not examined closely, but they appeared to exist largely in the keto-form, and, with the exception of (V; $R^1 = R^2 = R^3 = H$) did not give colours with aqueous iron(III) chloride. Compound (V; $R^1 = R^2 = R^3 = H$) was obtained from the ester (V; $R^1 = R^2 = H$, $R^3 = CO_2Et$) by alkaline hydrolysis and decarboxylation. The reported conditions [3] for the hydrolytic step failed. Removal of the ethoxycarbonyl group from the analogue (V; $R^1 = R^2 = Me$, $R^3 = CO_2Et$) without simultaneous loss of nitrogen was not achieved, but since this compound was stable to boiling water an alternative structure (VIII; $R^1 = R^2 = H$, $R^3 = Et$, $R^4 = CO{\cdot}NMe_2$) is considered to be unlikely.

Replacement of diethyl malonate by derivatives of ethyl acetoacetate in the foregoing synthesis did not yield the desired dihydrofurans. Not unexpectedly, reaction of ethyl γ-bromoacetoacetate [13,14] with triethylamine, as with sodium ethoxide,[5] gave diethyl 2,5-dihydroxycyclohexa-1,4-diene-1,4-dicarboxylate, and the only pure product isolated from ethyl γ-bromo-α-methylacetoacetate [15] was 3-methyltetronic acid.

Treatment of ethyl ethoxymagnesioacetoacetate with chloroacetyl chloride did not give 3-acetyl-2-ethoxyfuran-4(5*H*)-one; instead ethyl 4,5-dihydro-2-methyl-4-oxofuran-3-carboxylate (VII) was obtained by spontaneous decomposition of the acyclic intermediate, presumably (IX). Compound (VII) [16-18] (Becker's 'Substance B') has been obtained [16] from ethyl γγ-di-iododiacetoacetate and sodium thiosulphate.

5-Ethyltetronic acid and its 3-ethoxycarbonyl derivative were also prepared from the corresponding 5-ethylidenetetronic acids (XIII) and (X) (Scheme 2), but the last two compounds proved difficult to obtain in quantity.



SCHEME 2 Reagents: i, NaOH; ii, HCl; iii, H_2, Pd–C; iv, AcCl–$SnCl_4$; v, heat; vi, Br_2–HOAc; vii, Br_2–NaOAc

Fleming and Harley-Mason have described [19] two related syntheses of 3-ethoxycarbonyl-5-ethylidenetetronic acid (X). In the more convenient route the easily prepared diethyl αβ-dibromobutyryl malonate is cyclised (46%) with aqueous sodium hydroxide; subsequent hydrolysis and decarboxylation then yields (XIII) (70%).

In our hands cyclisation of the dibromobutyrylmalonate proved difficult. Under the reported conditions only traces of the product were isolable. A modified procedure gave reliable, but low yields (25—34%) on a 0·1—0·3 molar scale.

Although hydrogenation of 5-benzylidenetetronic acid and 3-ethoxycarboxyl-5-benzylidenetetronic acid over Adams catalyst in ethyl acetate gives [19] unsatisfactory results, 5-ethylidenetetronic acid (XIII) and 3-ethoxycarbonyl-5-ethylidenetetronic acid (X) were smoothly hydrogenated to the corresponding 5-ethyltetronic acids (VI; R = Et) and (III; R = Et) over palladium–carbon in ethanol.

As expected,[20] bromination of 5-ethylidenetetronic acid with bromine in acetic acid gave the 3-bromo-derivative (XIV). Bromination of 5-ethyltetronic acid

[13] M. Conrad, *Ber.*, 1896, **29**, 1042.
[14] K. von Auwers and E. Auffenberg, *Ber.*, 1917, **50**, 929.
[15] M. S. Kharasch, E. Sternfield, and F. R. Mayo, *J. Amer. Chem. Soc.*, 1937, **59**, 1655.
[16] A. von Becker, *Helv. Chim. Acta*, 1949, **32**, 1114.
[17] R. von Richter, *Helv. Chim. Acta*, 1952, **35**, 1115.
[18] R. E. Rosenkranz, K. Allner, R. Good, W. von Philipsborn, and C. H. Eugster, *Helv. Chim. Acta*, 1963, **46**, 1259.
[19] I. Fleming and J. Harley-Mason, *J. Chem. Soc.*, 1963, 4778.
[20] R. A. Raphael, *J. Chem. Soc.*, 1948, 1508.

to (XV) with bromine in chloroform was only satisfactory on a small scale, probably owing to the difficulty in removing all the evolved hydrogen bromide *in vacuo*; if this were not done subsequent crystallisation of the oil was difficult and intractable brown material was obtained. On a larger scale bromination in the presence of aqueous sodium acetate gave good results with this and other tetronic acids.

Acetylation of 5-ethyl- and 5-ethylidene-tetronic acids under Friedel–Crafts conditions [21] yielded the corresponding 3-acetyl derivatives (XVI) and (XII). Pyrolysis of the latter compound resulted in rearrangement to 2-acetyl-5-methylcyclopentane-1,3,4-trione (XI), obtained in wholly enolised form or forms. The n.m.r. spectrum revealed signals for six protons attached to carbon, all as methyl groups. Although the 2-*C*-methyl signal was a singlet at τ 8·24, the acetyl methyl group gave rise to two singlets of unequal area, at τ 7·75 and 7·81, ascribed to the presence of two isomers. A similar, reversible, rearrangement of 5-benzylidene-3-phenyltetronic acid has been discussed,[22] and a related rearrangement has been observed [23] in 3-acetyl-5-*p*-fluorobenzylidene-4-hydroxythiophen-2(5*H*)-one.

EXPERIMENTAL

M.p.s are corrected, light petroleum used had b.p. 60—80° unless stated otherwise, and solutions were dried with sodium sulphate. Purity checks on compounds by t.l.c. were carried out on silica GF 254 plates with benzene–ethanol–acetic acid (9 : 2 : 1) as developing solvent. U.v. spectra are reported for methanolic solutions. Molecular weight were obtained by low resolution mass spectroscopy (Hitachi RMU-6E instrument); n.m.r. spectra were obtained with a Perkin-Elmer R12 60 MHz or a Varian HA-100 spectrometer, and i.r. spectra with a Perkin-Elmer model 457 spectrometer.

Halogenoacylmalonates.—Method 1. *Diethyl chloroacetylmalonate* (II; X = Cl, R = H) (*cf.* ref. 4). Dry ethanol (25 ml) and carbon tetrachloride (0·5 ml) were added to magnesium (5·0 g). When the reaction became vigorous more ethanol (11 ml) was added and the mixture was heated under reflux for 1 h. Diethyl malonate (33·7 g) was added dropwise in 15 min (vigorous reaction). The mixture was boiled for 1 h, diluted dropwise with ether (100 ml), then boiled until a clear solution was obtained (2 h). The solution was treated dropwise at 0° during 1 h with chloroacetyl chloride (25·0 g). The mixture was then boiled for 30 min (colour green ⟶ yellow), then treated at 0° with ice and 3N-sulphuric acid (75 ml). The ethereal phase and ether washings of the aqueous phase were dried and evaporated *in vacuo* below 30° giving the product as a yellow oil (48·3 g, 97%) (Found: Cl, 14·5. Calc. for $C_9H_{13}ClO_5$: Cl, 15·0%). This product [and analogues (see later)] was stored at 0° and used in crude form.

Diethyl (α-*bromobutyryl*)*malonate* (II; X = Br, R = Et) was obtained similarly, from β-bromobutyryl bromide, as an oil (100%) (Found: Br, 26·1. $C_{11}H_{17}BrO_5$ requires Br, 25·9%). *Diethyl* (α-*chlorophenylacetyl*)*malonate* (II; X = Cl, R = Ph), from α-chlorophenylacetyl chloride, was an oil (96%) (Found: Cl, 10·4. $C_{15}H_{17}ClO_5$ requires Cl, 11·3%).

Method 2. *Diethyl* (α-*bromopropionyl*)*malonate* (II; X = Br, R = Me). α-Bromopropionyl bromide (43·2 g) was added dropwise, at a rate sufficient to maintain vigorous refluxing, to a stirred ethereal solution of diethyl ethoxymagnesiomalonate [prepared [12] from diethyl malonate (35·2 g)]. The mixture was then refluxed for 10 min and worked up as in method 1, giving the *product* as a yellow oil (55·1 g, 95%) (Found: Br, 26·2. $C_{10}H_{15}BrO_5$ requires Br, 27·1%).

Ethyl 4,5-*Dihydro*-2-*methyl*-4-*oxofuran*-3-*carboxylate* (VII). —Ethyl acetoacetate (27·4 g) was converted into the ethoxymagnesio-salt as described for diethyl ethoxymagnesiomalonate (method 1). After the addition of the ether and boiling for 2 h, the resulting thick white suspension did not appear to contain residual magnesium. Chloroacetyl chloride (25·0 g) was added at 0° and subsequent stages were carried out as already described, giving a yellow *oil* (22·6 g) (Found: Cl, 9·0. $C_8H_{11}ClO_4$ requires Cl, 17·2%). On storage overnight at 0° the dihydrofuran (6·3 g, 19%) separated as prisms, m.p. 74—76° [75·5—76° (from ether–light petroleum)] (Found: C, 56·2; H, 6·1. Calc. for $C_8H_{10}O_4$: C, 56·4; H, 5·9%) (lit.,[16] m.p. 75°), n.m.r. spectrum identical with that described.[18]

Ethyl 2-*Ethoxy*-4,5-*dihydro*-4-*oxofuran*-3-*carboxylates*.— (a) *Ethyl* 2-*ethoxy*-4,5-*dihydro*-4-*oxofuran*-3-*carboxylate* (IV; R = H).—A mixture of diethyl chloroacetylmalonate (50·9 g) and triethylamine (55 ml) in dry benzene (850 ml) was stirred at room temperature for 30 min, heated gradually to the b.p. during 45 min, then allowed to cool for 1 h. The precipitate was filtered off and the filtrate and benzene washings of the cake were concentrated to small volume *in vacuo*, giving two crops of the product (24·6 g), m.p. 86—91°, which formed prisms, m.p. 90—91·5° (22·4 g, 52%), from carbon tetrachloride. A sample for analysis (prisms from ether) had m.p. 92—93° (Found: C, 54·5; H, 6·0%; *M*, 200. Calc. for $C_9H_{12}O_5$: C, 54·0; H, 6·0%; *M*, 200), $\nu_{max.}$ (Nujol) 1730, 1670, and 1570br cm^{-1}, $\nu_{max.}$ ($CHCl_3$) 1738, 1695, and 1580 cm^{-1}.

In one preparation a dimorphic form [$\nu_{max.}$ (Nujol; Infracord) 1710br, 1580br, and 1570sh cm^{-1}], which soon reverted to the normal form, was obtained; $\lambda_{max.}$ 222 and 248 nm (ε 12,500 and 17,800), τ ($CDCl_3$) 5·35 (2H, s, CH_2), 5·38(q) and 5·72(q) (4H, 2 × O·CH_2), and 8·50(t) and 8·70(t) (6H, 2 × Me). The dihydrofuran was obtained in 13% yield by Benary's method (lit.,[3] m.p. 91—92°).

The following dihydrofurans were prepared similarly from the appropriate acid chloride.

(b) *Ethyl* 2-*ethoxy*-4,5-*dihydro*-5-*methyl*-4-*oxofuran*-3-*carboxylate* (IV; R = Me) [from diethyl (α-bromopropionyl)-malonate] was obtained in 83% yield, m.p. 74—75°, after one recrystallisation from carbon tetrachloride–light petroleum. A sample for analysis had m.p. 75—76° (Found: C, 56·5; H, 6·6%; *M*, 214. $C_{10}H_{14}O_5$ requires C, 56·1; H, 6·6%; *M*, 214), $\nu_{max.}$ (Nujol) 1730, 1663, and 1570br cm^{-1}, $\nu_{max.}$ ($CHCl_3$) 1731, 1692, and 1580 cm^{-1}, $\lambda_{max.}$ 222 and 248 nm (ε 11,900 and 19,000), τ ($CDCl_3$) 5·2 (2H, q, *J* 7 Hz, 5-H), 5·34(q) and 5·77(q) (4H, 2 × O·CH_2), 8·45 (3H, d, *J* 7 Hz, 5-Me), and 8·47(t) and 8·66(t) (6H, CH_2·CH_3).

(c) *Ethyl* 2-*ethoxy*-4,5-*dihydro*-4-*oxo*-5-*phenylfuran*-3-*carboxylate* (IV; R = Ph) [from diethyl (α-chlorophenylacetyl)-

[21] L. J. Haynes and J. W. M. Jamieson, *J. Chem. Soc.*, 1958, 4132.

[22] A. Schonberg and A. Sina, *J. Chem. Soc.*, 1946, 601.

[23] D. M. O'Mant, *J. Chem. Soc.* (*C*), 1968, 1501.

malonate] was pure (64%; m.p. 105—106°) after one crystallisation from ethanol (Found: C, 65·2; H, 5·8. $C_{15}H_{16}O_5$ requires C, 65·2; H, 5·8%), $\nu_{max.}$ (Nujol) 1740, 1685, and 1567 cm^{-1}, $\nu_{max.}$ ($CHCl_3$) 1738, 1700, and 1584 cm^{-1}, $\lambda_{max.}$ 221 and 251 nm (ε 18,600 and 14,700), τ ($CDCl_3$) 2·60 (5H, s, Ph), 4·40 (1H, C*H*Ph), 5·3(q) and 5·7(q) (4H, 2 × O·C*H*$_2$), and 8·45(t) and 8·70(t) (6H, 2 × CH$_2$·C*H*$_3$).

(d) *Ethyl 2-ethoxy-5-ethyl-4,5-dihydro-4-oxofuran-3-carboxylate* (IV; R = Et) [from diethyl (α-bromobutyryl)-malonate] (70%) had m.p. 58—62° after one crystallisation from ether–light petroleum (b.p. 30—40°); analytical sample, m.p. 62—64° (Found: C, 57·8; H, 7·2. $C_{11}H_{16}O_5$ requires C, 57·9; H, 7·1%), $\nu_{max.}$ (Nujol) 1736, 1670, and 1569 cm^{-1}, $\nu_{max.}$ ($CHCl_3$) 1736, 1697, and 1580 cm^{-1}, $\lambda_{max.}$ 221 and 248 nm (ε 13,400 and 18,100), τ ($CDCl_3$) 5·38 (1H, X of ABX, C*H*·CH$_2$·CH$_3$), 5·4(q) and 5·7(q) (4H, 2 × O·C*H*$_2$), *ca.* 8·05 (2H, m, CH·C*H*$_2$·CH$_3$), 8·5(t) and 8·7(t) (6H, 2 × O·CH$_2$·C*H*$_3$), and 9·0 (3H, t, CH·CH$_2$·C*H*$_3$).

Ethyl 2-Amino-4,5-dihydro-4-oxofuran-3-carboxylate (V; R^1 = R^2 = H, R^3 = CO_2Et).—A solution of diethyl chloroacetylmalonate (12·0 g) and triethylamine (10 ml) in benzene (250 ml) was heated gradually to the b.p. during 45 min, then allowed to cool (1 h). A stream of dry ammonia was passed through the mixture at 0° for 1 h. The precipitated product [6·61 g; m.p. *ca.* 233° (decomp.)] crystallised from ethanol as prisms, m.p. 244° (decomp.) [lit.,[2] 243° (decomp.)] (Found: C, 48·9; H, 5·3; N, 8·2. Calc. for $C_7H_9NO_4$: C, 49·1; H, 5·3; N, 8·2%), $\nu_{max.}$ (Nujol) 3398mw, 3285w, 1845w,sh, 1704m, 1664s, 1635vs, and 1529ms,br cm^{-1}, $\lambda_{max.}$ 245 nm (ε 25,200), τ [$(CD_3)_2SO$] 1·71br (2H, NH$_2$), 5·52 (2H, s, CH$_2$), 5·85 (2H, q, O·CH$_2$), and 8·81 (3H, t, Me). The compound gave no colour with aqueous iron(III) chloride.

Ethyl 2-Dimethylamino-4,5-dihydro-4-oxofurancarboxylate (V; R^1 = R^2 = Me, R^3 = CO_2Et).—Repetition of the foregoing sequence with dimethylamine instead of ammonia, then recovering the product by evaporating the reaction mixture and extracting the residue with ether, gave the *product* as prisms, m.p. 53—54·5° (from cyclohexane–benzene) (Found: C, 54·3; H, 6·7; N, 7·0. $C_9H_{13}NO_4$ requires C, 54·3; H, 6·6; N, 7·0%), $\nu_{max.}$ (Nujol) 1697ms, 1670s, and 1656m,sh cm^{-1}, $\lambda_{max.}$ 263 nm (ε 25,100), τ ($CDCl_3$) 5·47 (2H, s, CH$_2$), 5·71 (2H, q, O·CH$_2$), 6·81 (6H, s, NMe$_2$), and 8·66 (3H, t, Me).

The following derivatives were obtained similarly (starting amine added at room temperature).

(i) Ethyl 4,5-dihydro-4-oxo-2-phenylhydrazinofuran-3-carboxylate (V; R^1 = H, R^2 = NHPh, R^3 = CO_2Et) (from phenylhydrazine) crystallised from benzene–ethyl acetate in prisms and needles, m.p. 188—189·5° (lit.,[7] 188—189°) (Found: C, 59·5; H, 5·7; N, 10·4. Calc. for $C_{13}H_{14}N_2O_4$: C, 59·5; H, 5·4; N, 10·7%).

(ii) *Ethyl 4,5-dihydro-2-isopropylamino-4-oxofuran-3-carboxylate* (V; R^1 = H, R^2 = Pr^i, R^3 = CO_2Et) (from isopropylamine) formed needles, m.p. 123—124° (from light petroleum) (Found: C, 56·7; H, 7·0; N, 6·4. $C_{10}H_{15}NO_4$ requires C, 56·3; H, 7·1; N, 6·6%). This compound was unchanged by refluxing in water for 5 h and only slightly (t.l.c.) attacked on refluxing with 0·02N-hydrochloric acid for 2 h.

(iii) *Ethyl 2-(diethylamino)ethylamino-4,5-dihydro-4-oxofuran-3-carboxylate* (V; R^1 = H, R^2 = [CH$_2$]$_2$·NEt$_2$, R^3 = CO_2Et) (from 2-diethylaminoethylamine) formed plates, m.p. 119—121° (from light petroleum) (Found: C, 57·5; H, 8·1; N, 10·7. $C_{13}H_{22}N_2O_4$ requires C, 57·8; H, 8·2; N, 10·4%).

(iv) *Ethyl 2-allylamino-4,5-dihydro-4-oxofuran-3-carboxylate* (V; R^1 = H, R^2 = CH$_2$·CH:CH$_2$, R^3 = CO_2Et) (from allylamine) formed plates, m.p. 85—86° (from light petroleum) (Found: C, 57·0; H, 6·1; N, 6·8. $C_{10}H_{13}NO_4$ requires C, 56·9; H, 6·2; N, 6·6%).

2-Aminofuran-4(5H)-one (V; R^1 = R^2 = R^3 = H).—A solution of ethyl 2-amino-4,5-dihydro-4-oxofuran-3-carboxylate (30·8 g) in 2N-potassium hydroxide (900 ml) was stored at room temperature for 3 days, then concentrated *in vacuo* to *ca.* 250 ml, and diluted with ethanol (1400 ml). The precipitated salt was washed with alcohol and dissolved in water (150 ml), and the solution was acidified at 0° with 3N-hydrochloric acid. The solid which separated was washed with a small volume of water and suspended in water (450 ml), and the mixture was heated under nitrogen, first on steam (30 min), then under reflux (20 min). The resulting solution was evaporated *in vacuo* and the dry residue was extracted with cold methanol (400 ml). Evaporation of the extract gave the product (12·1 g), which crystallised from methanol–ether in prisms (10·4 g), m.p. 215—217° (decomp.) (lit.,[3] 211°) (Found: C, 48·6; H, 5·0; N, 14·1%; *M*, 99. Calc. for $C_4H_5NO_2$: C, 48·5; H, 5·1; N, 14·1%; *M*, 99), p*K* in water >7, $\nu_{max.}$ (Nujol) 3400w, 3270m, 3030m, 1681mw, 1637m, and 1569br cm^{-1}, $\lambda_{max.}$ 258 nm (ε 27,600), τ [$(CD_3)_2SO$] 2·2br (2H, NH$_2$ or NH and OH) and 5·62 (3H, s, CH$_2$ and CH). The compound gave an orange-brown colour with aqueous iron(III) chloride.

Hydrolysis of Ethyl 2-Ethoxy-4,5-dihydro-4-oxofuran-3-carboxylates.—(a) *To tetronic acids.* (i) *Tetronic acid* (VI; R = H).—Ethyl 2-ethoxy-4,5-dihydro-4-oxofuran-3-carboxylate (4·0 g; m.p. 90—91°) was dissolved in cold water (40 ml), and 0·3N-barium hydroxide solution (330 ml) was added below 21° (cooling). After storage for 5 days at room temperature the precipitated barium salt was collected, washed with water and alcohol, dried, and suspended in water (75 ml). N-Sulphuric acid (38·0 ml) was added and the mixture was stored at room temperature for 1 h with occasional stirring, then filtered. Evaporation of the filtrate gave almost colourless tetronic acid (1·8 g, 90%), m.p. 138—140°, showing only one spot on t.l.c.

Sublimation or crystallisation raised the m.p. to 140—141° (Found: C, 48·1; H, 4·0. Calc. for $C_4H_4O_3$: C, 48·0; H, 4·0%) (lit.,[24] m.p. 139—140°; lit.,[25] 141°).

(ii) *5-Ethyltetronic acid* (VI; R = Et). A solution of ethyl 2-ethoxy-5-ethyl-4,5-dihydro-4-oxofuran-3-carboxylate (1·50 g) in water (15 ml) was stored at room temperature for 18 h, then treated with an excess of 0·3N-barium hydroxide. The barium salt (1·82 g), collected after 5 days, was decomposed with 99% of the theoretical amount of N-sulphuric acid, and the product was recovered as in (i) giving the tetronic acid (714 mg, 85%), m.p. 124—128°, raised to 129—130° by sublimation *in vacuo* or crystallisation (prisms) from ethyl acetate–light petroleum (Found: C, 56·6; H, 6·2. Calc. for $C_6H_8O_3$: C, 56·2; H, 6·2%) (lit.,[26] m.p. 127—129°).

(iii) *5-Methyltetronic acid* (VI; R = Me). Ethyl 2-ethoxy-4,5-dihydro-5-methyl-4-oxofuran-3-carboxylate (1·30 g) was stored with aqueous 2·25N-potassium hydroxide (20 ml) for 5 days at room temperature. The solution was acidified with concentrated hydrochloric acid, heated

[24] L. A. Duncanson, *J. Chem. Soc.*, 1953, 1207.
[25] L. von Wolff, *Annalen*, 1896, **291**, 226.
[26] L. Pons and H. Veldstra, *Rec. Trav. chim.*, 1955, **74**, 1217.

briefly on steam, then extracted six times with ethyl acetate. Recovery from the extract gave the tetronic acid (621 mg, 89%), m.p. 118—120°, not raised by recrystallisation. Material obtained [11] from acetyl-lactyl chloride and diethyl ethoxymagnesiomalonate had the same m.p. (lit.,[27] 117—119°; lit.,[24] 118°).

(iv) 5-*Phenyltetronic acid* (VI; R = Ph). Ethyl 2-ethoxy-4,5-dihydro-4-oxo-5-phenylfuran-3-carboxylate (2·76 g) was hydrolysed with potassium hydroxide as described in (iii). The acidified solution, after being heated briefly on steam and cooled to 0°, deposited the tetronic acid (1·64 g, 93%), m.p. 120—126°, raised to 127° by recrystallisation from water, and identical with an authentic specimen [4] (lit.,[27] m.p. 127·5—128·5; lit.,[4] 127°).

(b) *To ethoxycarbonyltetronic acids.* (i) 3-*Ethoxycarbonyltetronic acid* (III; R = H). An aqueous solution of ethyl 2-ethoxy-4,5-dihydro-4-oxofuran-3-carboxylate was stored at room temperature for 18 h. Evaporation of the solution *in vacuo* gave 3-ethoxycarbonyltetronic acid (93%), m.p. 121—123° (rapid heating) or *ca.* 117° (slow heating) (Found: C, 48·8; H, 4·7. Calc. for $C_7H_8O_5$: C, 48·8; H, 4·7%) (lit.,[2] m.p. 124—125°; lit.,[4] 125°).

Hydrolysis of the crude ester by Reuter's method [5] gave crude tetronic acid (81%), m.p. 133—137°.

The following esters were obtained analogously.

(ii) 3-Ethoxycarbonyl-5-methyltetronic acid (III; R = Me) (from ethyl 2-ethoxy-4,5-dihydro-5-methyl-4-oxofuran-3-carboxylate) (95%), m.p. 87—89°, raised to 89° by crystallisation from ethyl acetate–light petroleum (Found: C, 51·8; H, 5·5. Calc. for $C_8H_{10}O_5$: C, 51·6; H, 5·4%) (lit.,[3,5] m.p. 88—89°).

(iii) 3-*Ethoxycarbonyl-5-ethyltetronic acid* (III; R = Et) (from ethyl 2-ethoxy-5-ethyl-4,5-dihydro-4-oxofuran-3-carboxylate) (100%), m.p. 80—83°. Crystallisation from ethyl acetate gave prisms, m.p. 85—87°, identical with material obtained by a different method (see later) (Found: C, 53·7; H, 6·0. $C_9H_{12}O_3$ requires C, 54·0; H, 6·0%), $\lambda_{max.}$ 223 and 249 nm (ε 13,000 and 16,500).

(iv) 3-*Ethoxycarbonyl-5-phenyltetronic acid* (III; R = Ph). A suspension of ethyl 2-ethoxy-4,5-dihydro-4-oxo-5-phenylfuran-3-carboxylate (5·0 g) in aqueous ethanol (3 : 1; 150 ml) was stirred at room temperature until dissolution was complete (8 h). After a further 2 days concentration to small volume *in vacuo* gave the ethoxycarbonyltetronic acid (3·85 g, 86%), m.p. 139—141° identical with an authentic sample [4] (lit.,[4,27] m.p. 140°).

3-*Ethoxycarbonyl-5-ethylidenetetronic Acid* (X).—2·5N-Sodium hydroxide (176 ml), pre-warmed to 25°, was added rapidly to crude diethyl (αβ-dibromobutyryl)malonate [prepared [19] from diethyl crotonoylmalonate (33·4 g)]. The mixture was stirred without cooling while the temperature rose spontaneously to 45° during 10 min. After a further 3 min, during which no further rise in temperature took place, water (260 ml; 20°) was added and the solution was stored at room temperature for 6 h. The mixture was washed with ether, then acidified below 10° with an excess of concentrated hydrochloric acid. When the pH reached 1—2 an emulsion formed; addition of more acid caused rapid separation of the product as a bulky crystalline precipitate. This was collected, washed with cold water, and dried *in vacuo* giving oily needles, mainly melting at 120—125°. A further 1·0 g was obtained by recovery from the aqueous mother liquor in chloroform and pressing the oily product on a porous plate.

The crude product (34·9 g) crystallised from benzene–light petroleum giving the ester (34%) as needles: (i) 14·4 g, m.p. 134—136°; (ii) 4·9 g, m.p. 132—135° (lit.,[19] 134—136°) (Found: C, 54·7; H, 5·1. Calc. for $C_9H_{10}O_5$: C, 54·5; H, 5·1%). The n.m.r. and i.r. spectra agreed with those reported [19] except that there was no band at 1690 cm^{-1}.

The recrystallised ester was stored unchanged at room temperature for several months, but impure material soon decomposed above 0°.

5-Ethylidenetetronic acid (XIII), obtained [19] from the foregoing ester, had m.p. 190—192° (decomp.) (Found: C, 56·9; H, 4·9. Calc. for $C_6H_6O_3$: C, 57·2; H, 4·8%) [lit.,[19] m.p. 182—185° (decomp.)].

The O-*benzoate* formed prisms, m.p. 138° (from ethyl acetate–light petroleum) (Found: C, 67·6; H, 4·4. $C_{13}H_{10}O_4$ requires C, 67·8; H, 4·4%).

5-*Ethyltetronic Acid.*—A mixture of 5-ethylidenetetronic acid (630 mg), ethanol (5 ml), and 5% palladium–carbon (0·3 g) was shaken in hydrogen at room pressure and temperature until uptake (1·0 mol. equiv.) ceased. Work-up gave the tetronic acid (100%), m.p. 126—129° (raised to 129—130° by recrystallisation).

3-*Ethoxycarbonyl-5-ethyltetronic Acid.*—Hydrogenation of 3-ethoxycarbonyl-5-ethylidenetetronic acid similarly gave the product (95%), m.p. 80—84° (raised to 86—88° by recrystallisation).

3-*Bromo-5-ethyltetronic Acid* (XV).—Bromine (3·12 g) was added dropwise at 0° to a stirred solution of 5-ethyltetronic acid (2·56 g) and sodium acetate trihydrate (5·4 g) in water (15 ml). The resulting solution was acidified at 0° with concentrated hydrochloric acid and the *product* (1·0 g; m.p. 101—103°) was collected. Recovery from the mother liquor in ethyl acetate gave an oil from which a second crop of product (1·2 g; m.p. 101—102°) was obtained by crystallisation from cyclohexane–light petroleum. A sample for analysis had m.p. 103—104° (Found: C, 35·2; H, 3·7. $C_6H_7BrO_3$ requires C, 34·8; H, 3·4%), $\lambda_{max.}$ 260 nm (ε 15,700).

Bromination in chloroform sometimes gave a higher yield (71%) on a small scale, but was unsatisfactory on a large scale.

3-*Bromo-5-ethylidenetetronic Acid* (XIV).—A stirred suspension of 5-ethylidenetetronic acid (1·26 g) in glacial acetic acid (10 ml) was treated dropwise at room temperature with a 16% w/v solution (9·8 ml) of bromine in acetic acid. Concentration of the resultant suspension *in vacuo* over sodium hydroxide gave the sparingly soluble *product* (693 mg), m.p. 190° (decomp.), which crystallised from ethyl acetate–light petroleum or benzene–ethanol in plates (Found: C, 35·6; H, 2·8; Br, 38·9. $C_6H_5BrO_3$ requires C, 35·2; H, 2·5; Br, 39·0%), $\lambda_{max.}$ 246 and 309 nm (ε 14,100 and 8940), τ [$(CD_3)_2SO$] 1·7 (1H, s, OH), 4·15 (1H, q, *J* 8 Hz, CH), and 8·20 (3H, d, *J* 8 Hz, Me).

3-*Acetyl-5-ethylidenetetronic Acid* (XVI).—Tin(IV) chloride (3·0 ml) was added to a mixture of 5-ethylidenetetronic acid (2·52 g) and acetyl chloride (6·0 ml) below −10°. The mixture was allowed to warm to room temperature, then heated under reflux on steam for 4 h, giving a black tar. This was mixed with 5N-hydrochloric acid and chloroform below 5° (hand-stirred), the liquids were decanted, and the residual tar was extracted twice more with the acid and chloroform. The chloroform phase was separated, combined with chloroform washings of the aqueous phase, and extracted with aqueous sodium hydrogen carbonate. The

[27] R. von Anschütz and R. Böcker, *Annalen*, 1909, **368**, 53.

alkaline extract, on acidification with hydrochloric acid deposited a solid. This, combined with more product (total 1·1 g) recovered by chloroform extraction of the aqueous mother liquor, crystallised from ethyl acetate–light petroleum in *prisms* (950 mg), m.p. 123—125° (raised to 124—126° by recrystallisation) (Found: C, 56·9; H, 4·8%; *M*, 168. $C_8H_8O_4$ requires C, 57·1; H, 4·8%; *M*, 168), $\lambda_{max.}$ 251 and 294 nm (ε 20,300 and 11,500), τ ($CDCl_3$) −0·8 (1H, s, OH), 4·0 (1H, q, *J* 8 Hz, C*H*·CH_3), 7·40 (3H, s, CO·CH_3), and 7·95 (3H, d, *J* 8 Hz, CH·C*H*$_3$).

3-*Acetyl-5-ethyltetronic Acid* (XII).—Acetylation of 5-ethyltetronic acid as described for 5-ethylidenetetronic acid gave the *ketone* (66%), m.p. 54—57°, raised to 58—59° by recrystallisation (needles) from light petroleum (b.p. 40—60°) (Found: C, 56·1; H, 6·0. $C_8H_{10}O_4$ requires C, 56·5; H, 5·9%), $\lambda_{max.}$ 230 and 263 nm (ε 14,500 and 16,400).

Pyrolysis of 3-*Acetyl-5-ethylidenetetronic Acid* (XII).—The tetronic acid (80 mg), contained in a small bulb connected by a capillary tube to an open, wider tube which served as a condenser, was heated at 240° for 2 h. Black tar remained in the bulb and yellow crystals (27 mg; m.p. 215—225°) sublimed into the condenser. In an open system only starting material sublimed. Crystallisation of the yellow product from ethyl acetate gave an enolised form, or mixture of forms, of 2-*acetyl-5-methylcyclopentane*-1,3,4-*trione* (XI) as yellow prisms, m.p. 230—232° (sealed tube) (Found: C, 57·2; H, 4·6%; *M*, 168. $C_8H_8O_4$ requires C, 57·1; H, 4·8%; *M*, 168), $\nu_{max.}$ (Nujol) 3160br, 1725m, 1673m, and 1622s cm^{-1}, $\lambda_{max.}$ 256 and 308 nm (ε 17,000 and 10,200), τ [$(CD_3)_2SO$] 7·75 (minor) and 7·81 (major) (3H, 2 × s, Ac), and 8·24 (3H, s, Me).

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