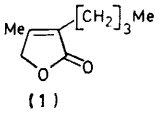
Metabolites of the Higher Fungi. Part 19.[1] Serpenone, 3-Methoxy-4-methyl-5-prop-1-enylfuran-2(5*H*)-one, a new γ-Butyrolactone from the Fungus *Hypoxylon serpens* (Barrons strain) (Persoon ex Fries)Kickx

By **John R. Anderson** and **Raymond L. Edwards,*** School of Chemistry, University of Bradford, Bradford, W. Yorkshire BD7 1DP
Anthony J. S. Whalley, Department of Biology, Liverpool Polytechnic, Liverpool L3 3AF

Culture solutions of the fungus *Hypoxylon serpens* (Barrons strain) contain a new butyrolactone as the major metabolite, which has been identified as 3-methoxy-4-methyl-5-prop-1-enylfuran-2(5*H*)-one (2), and small quantities of the reduced analogue, 3-methoxy-4-methyl-5-propylfuran-2(5*H*)-one (3); the structures have been established by synthesis of compound (3). A new rapid synthesis of the isomeric 4-methoxy-3,5-disubstituted analogues is described and the two groups of compounds are compared spectroscopically.

In a previous paper [1] we reported the isolation, structure determination, and synthesis of a new γ-butyrolactone (1) from the fungus *Hypoxylon serpens* (Persoon ex Fries) Kickx. *Hypoxylon serpens* is known to be a very variable species [2,3] and one isolate obtained from soil in Ontario, Canada by G. L. Barron produces mature perithecia in culture. This feature is quite exceptional since very few species of *Hypoxylon* (Bulliard ex Fries) fruit in culture and at present this is the only known strain of *H. serpens* to do so. An examination of cultures of the Barrons strain (A.T.C.C. 16078) has yielded an odoriferous oil which we have characterised as compound (2). The fungus grew rapidly on either malt extract or potato dextrose–yeast (PDY) media, but significant quantities of compound (2), admixed with a little of compound (3)



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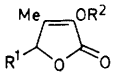
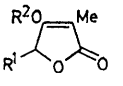
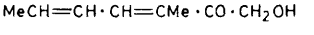


(2) R^1 = MeCH=CH, R^2 = Me
(3) R^1 = $MeCH_2CH_2$, R^2 = Me
(9) R^1 = $MeCH_2CH_2$, R^2 = H
(10) R^1 = CCl_3, R^2 = H
(11) R^1 = $MeCHClCH_2$, R^2 = H
(12) R^1 = $MeCHClCH_2$, R^2 = Me



(4) R^1 = MeCH=CH, R^2 = Me
(5) R^1 = $MeCH_2CH_2$, R^2 = Me
(8) R^1 = MeCH=CH, R^2 = H
(20) R^1 = $MeCH_2CH_2$, R^2 = H



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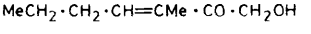


(7)

were only produced on PDY. Production of the metabolites began after about three weeks growth and their formation was indicated by the development of a celery-like odour and the production of a brown pigment in the medium. Concurrently, mature perithecia developed.

The lactone (2), $C_9H_{12}O_3$, M^+ 168, b.p. 90—92 °C/1.5 mmHg, $[\alpha]_D$ −59°, is a colourless oil of characteristic smell which dissolves slowly in cold, dilute aqueous sodium hydroxide with decomposition. A small quantity of compound (3) (M^+ 170), which was present in the crude extract, is much more stable and can be recovered substantially unchanged on acidification. This latter property of compound (3) and the presence of an i.r. band at ν 1 762 cm^{-1} in both compounds indicates the presence of a γ-lactone ring. The ^1H n.m.r. spectrum of compound (2) shows the presence of three different Me groups which absorb at δ 1.76 (d, *J* 7 Hz, *Me*CH=CH), 1.87 (s, C=CMe), and 3.93 (s, OMe). A single proton sextet centred at δ 5.94 (Me*CH*=CH), which consists of an overlapping double quartet (*J* 7 and 16 Hz), indicates a *trans*-arrangement of the unsaturated protons. The remaining two protons (=*CHCH*O) appear as an overlapping multiplet between δ 5.3 and 4.92. The methyl signals at δ 1.76 and 1.87 appear as double peaks of similar intensity (1.5 Hz separation), which may be ascribed to the presence of two isomers (see later). U.v. absorption of compound (2) occurs at λ 227 nm, typical of β-unsaturated butenolides.[4] The nature of the side-chain was confirmed by a controlled catalytic hydrogenation over platinum. Absorption of 1 mol equiv. of hydrogen gave compound (3) which has the expected ^1H n.m.r. spectrum of a 4-propyl substituted butenolide [δ 0.96 (3 H, t, *Me*CH_2), 1.40 (4 H, m, Me*CH_2*CH_2), 1.92 (3 H, s, C=CMe), 3.92 (3 H, s, OMe), and 4.7 (1 H, t, CH_2*CH*O)]. A weak signal at δ 1.40 confirmed the presence of small quantities of this material in the isolated culture lactone.

The i.r., u.v., and ^1H n.m.r. spectral data could also be ascribed to the isomeric lactones (4) and (5) and since 3-hydroxybut-2-enolides occur quite commonly as natural products and often have distinctive odours [5] it seemed logical to assign structure (4) to the new metabolite. However, the action of hot dilute acid over an extended period resulted in only partial demethylation whereas 3-methoxy-derivatives are reported to demethylate readily. Also, the oily product obtained from lithium aluminium hydride reduction of compound (2) shows ^1H n.m.r. absorptions at δ 1.9 (3 H, d, *Me*=CH=CH), 1.98 (3 H, s, Me=C=), 3.4 (1 H, br, CH_2OH, exchangeable with D_2O), 4.6 (2 H, s, CH_2OH), 6.68—6.12 (2 H, m, CH=CH), 7.0 (1 H, d, *J* 8 Hz, CH=CHC*H*), compatible with the formation of the α-keto-unsaturated

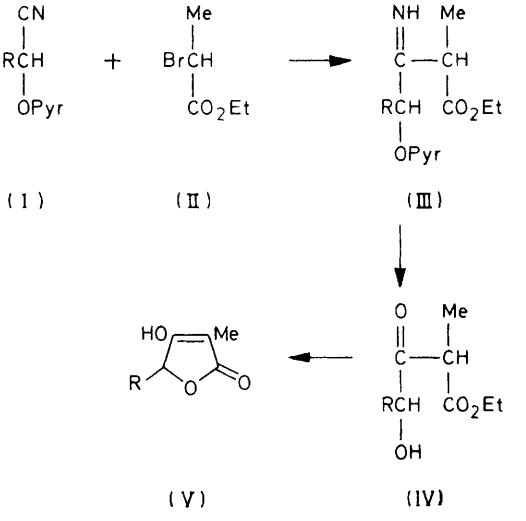
alcohol (6). Similarly, the reduced natural product (3) gave the corresponding reduced alcohol (7), which gave an oily acetate showing the expected δ 0.51 primary proton shift and i.r. absorption at $\nu_{max.}$ 1 749, 1 690, and 1 645 cm^{-1}. Such products could only arise from the 2-methoxy-lactones of type (2) and final proof of the structure was obtained by synthesis (see below).

For comparative purposes it was decided to synthesise the unsaturated butenolide (4) and the saturated butenolide (5). Methods available for the synthesis of 3-hydroxybut-2-enolides and their methyl ethers are numerous, but several of them are limited to the preparation of 2- or 4-monosubstituted compounds.[6] Of the methods available for the synthesis of 2,4-disubstituted compounds, most are restricted to the preparation of compounds which bear either saturated alkyl or aryl groups at the 4-position or to 4-alkylidene derivatives where the unsaturated double bond is exocyclic to the ring.[7] Interest in the latter group of compounds has been stimulated over the past decade by their widespread occurrence as natural products in fungi, marine organisms, and the higher plants.

The 3-hydroxy-2-methyl-4-propylbutenolide (20) was readily prepared by cyclisation of the halogenated β-keto-ester, but the presence of the prop-1-enyl group in compound (8) at C-4 ruled out the synthesis of this analogue by this route. Also, an attempted Haines-type synthesis [8] involving an internal Claisen ester condensation of the α-acyloxyester derived from ethyl 2-hydroxypent-3-enoate and ethyl 2-carboxypropionate failed to yield any of the desired product in the presence of a variety of condensing agents.

The reaction between n-alkyl nitriles and 2-bromo-esters in the presence of zinc to yield β-keto-esters [9] appeared to offer a route to the required tetronic acid (8). It was envisaged that reaction between a cyanohydrin pyranyl ether (I) and a 2-bromo-ester (II) in the presence of zinc would produce an intermediate imine (III); this, on hydrolysis, would yield a 4-hydroxy-3-keto-ester (IV) capable of cyclising to yield a 2,4-disubstituted-3-hydroxybutenolide (V) (Scheme). The nature of the 2- and 4-substituents would thus be variable and would depend on the use of the appropriate bromo-ester (I) and cyanohydrin (II).

The crotonaldehyde cyanohydrin pyranol ether, 1-(tetrahydropyranyloxy)but-2-enyl cyanide (I; R = Me-CH=CH), reacted readily with ethyl 2-bromopropionate (II) in the presence of zinc to give a product which was readily hydrolysed by dilute acid at room temperature over 12 h with spontaneous cyclisation to yield the tetronic acid (8). By varying the cyanohydrin we have shown that yields tend to improve as the size of the 4-substituent is increased. Variation of the 2-bromo-ester showed that ethyl 2-bromoacetate was unsuitable in this reaction, but ethyl 2-bromopropionate reacted with a wide range of cyanohydrins and a single experiment employing ethyl 2-bromobutyrate gave a satisfactory yield of the tetronic acid. The failure of ethyl bromoacetate in this reaction parallels observations made by other workers [9] during the preparation of β-keto-esters. No attempt has been made to optimise the conditions required to obtain maximum yield in this reaction; the yield varied between 10 and 20% when the cyanohydrin pyranyl ethers derived from crotonaldehyde, acetaldehyde, propionaldehyde, butyraldehyde, benzaldehyde, and acetone were treated with ethyl 2-bromopropionate. The speed, ready accessibility of the starting materials, and ease of purification makes this a useful method for the preparation of 2,4-disubstituted 3-hydroxybutenolides.



Pyr = tetrahydropyranyl

SCHEME

The ^1H n.m.r. spectra of the natural product (2) and the reduced natural product (3) are very similar to those of the isomeric synthetic methyl ethers (4) and (5); in both cases the major difference appears in the chemical shift of the OMe protons which absorb at lower field (δ 0.1) in the synthetic compounds. Also, the mass spectra fragmentation patterns are similar, but not identical. The synthetic compound (5) base peak appears at *M* 99, compared with *M* 71 in the reduced natural product (3), and appears at *M* 99 in compound (4) and *M* 69 in the natural product (2) (Table). The most striking difference between the synthetic and naturally occurring compounds is observed in their i.r. spectra; the intensity of the

(2)	(4)	(5)	(3) [a]	(3) [b]	(13)	(15)	(14)
		170 (12)	170 (26)	170 (26)			
168 (53)	168 (8)				168 (80)	168 (59)	
							154 (13)
153 (35)	153 (11)				153 (100)	153 (55)	
140 (41)	140 (64)					140 (100)	
		127 (56)	127 (46)	127 (46)			
		126 (24)					126 (40)
125 (64)	125 (11)				125 (30)	125 (21)	
99 (29)	99 (100)	99 (100)	99 (37)	99 (37)		99 (14)	
					98 (20)	98 (24)	
						97 (14)	
71 (47)	71 (14)	71 (12)	71 (100)	71 (100)			71 (46)
	70 (17)						
69 (100)	69 (28)				69 (32)		69 (16)
						68 (34)	68 (37)
	59 (19)	59 (38)	59 (38)	59 (38)			56 (100)
					55 (60)		55 (51)
						54 (62)	

[a] From reduction of compound (2). [b] Synthetic.

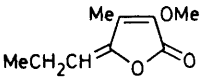
absorption band in the ν 1 650—1 700 cm^{-1} region for compounds (2) and (3) is low compared with that of the lactone carbonyl absorption. In both of the synthetic methyl ethers (4) and (5) and in all the 2,4-disubstituted 3-hydroxy- or 3-methoxy-butenolides the intensity of the ν 1 650—1 700 cm^{-1} band is comparable with or greater than that of the lactone absorption. From these observations it is apparent that the natural products are not 3-methoxybutenolides.

Several methods are available for the synthesis of 2-hydroxybutenolides and much work has been directed towards establishing the factors which govern the stability of the substituted ring system towards acids and alkali.[4,10,17] The ring system has also been of interest in the study of cephalosporin type systems [18,19] and also in the food flavouring industry.[20] Most of the known, simple 3,4-dialkylated compounds have a persistent caramel or curry-like odour and are prepared either by decarboxylation of the base-catalysed condensation product derived from 2-oxo-3-alkylbutanedioates and aldehydes [4,20] or by the condensation of α-keto-acids or -esters with aldehydes in the presence of sulphuric acid.[21]

The product derived from the reaction of diethyl 2-oxomethylbutanedioate and butanal gave, on decarboxylation, the 2-hydroxybutenolide (9) as an odoriferous oil. Methylation of this with diazomethane gave the methyl ether (3) which shows i.r., u.v., ^1H n.m.r., and mass spectra identical with that of the reduced natural product. However, attempts to prepare the natural product (2) by a similar condensation using crotonaldehyde have failed and the reaction between crotonaldehyde and 2-oxobutyric acid gave only resinous material.

Ritter [12] has shown that trichloroacetaldehyde can be successfully used to produce the 4-trichloromethyl lactone (10) and a similar condensation using 3-chlorobutyraldehyde followed by dehydrohalogenation appeared to offer an alternative approach to the desired natural product. 3-Chloro- and 3-bromo-butyraldehyde are unstable compounds which polymerise readily. Each was prepared by hydrogen halide addition to crotonaldehyde [22,23] and used without purification. The bromo-compound was unstable in the presence of pyridine and yielded a copious precipitate of pyridine hydrobromide on mixing the reactants, but the chloro-compound was more stable and reacted normally with the ester in the presence of pyridine to yield a product which, on acid hydrolysis, gave the chloro-lactone (11) as an oily solid which decomposed rapidly at room temperature within 12 h. The methyl ether (12) was more stable and shows ^1H n.m.r. peaks at δ 1.8—2.4 (2 H, m, $CHClCH_2CHO$), 4.04 (3 H, s, OMe), 4.4 (1 H, m, $MeCHCl$-CH_2), 5.07 (1 H, dd, *J* 8 and 1.5 Hz, CH_2CHO), but the methyl signals at δ 1.63 (3 H, d, *J* 7 Hz, *Me*CHCl) and 2.01 (3 H, s, MeC=) consist of closely spaced double signals due to the presence of two isomers. P.l.c. gave the predominant isomer as a solid of low melting point; ^1H n.m.r. ($CDCl_3$) δ 1.63 (3 H, d, *J* 7 Hz, *Me*CHCl) and 2.02 (3 H, s, MeC=) and the other was obtained as an oil; δ 1.59 (3 H, d, *J* 7 Hz, *Me*CHCl) and 2.01 (3 H, s, MeC=). The isomers presumably arise at the 4-chiral centre of the lactone ring since a similar doubling of signals is also observed in the naturally occurring lactone (2). However, in the latter case we have been unable to resolve the mixture by chromatography.

Attempts to dehydrohalogenate compound (12) with bases such as triethylamine and quinoline were unsuccessful and gave unchanged starting material as the only identifiable product. However, in boiling benzene over 48 h in the presence of 1,5-diazabicyclo[4.3.0]non-5-



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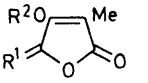
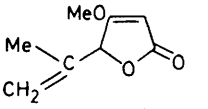


(14) R^1 = $MeCH_2CH$, R^2 = H
(15) R^1 = $MeCH_2CH$, R^2 = Me



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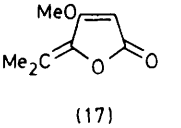

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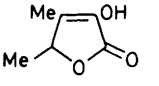

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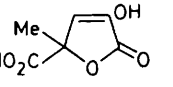

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ene (DBN) a small yield of a new lactone (13) was obtained, which results from dehydrohalogenation and isomerisation of the parent compound; a small quantity of methoxymethylmaleic anhydride was also obtained. Likewise, treatment of the unsaturated tetronic acid (8) with DBN gave the unsaturated isomeric lactone (14) in 45% yield, and the methyl ether (4) gave the isomeric ether (15) and the demethylated lactone (14). These results suggested that the natural product (2) should also undergo rearrangement under similar conditions. This was found to be the case and the product was identical with compound (13); again, methoxymethylmaleic anhydride was produced during the reaction. There was no evidence for the formation of the latter compound from either compound (8) or (4). Only one isomer of compound (15) was formed during the isomerisation and this is assigned the *Z*-configuration by comparison with the two isomers prepared by the action of propanal on 3-methoxy-4-methyl-5(2*H*)-oxofuran-2-yltriphenylphosphonium bromide.[5] Similarly, but not proven, the *Z*-configuration is assigned to the lactone (13) [δ 5.05 (t, CH_2CH=)], obtained by dehydrohalogenation of compound (12). These rearrangements are similar to that undergone by the lactone (16) to yield compound (17) on treatment with a weak base such as ammonia, and observed during the synthesis of penicillic acid.[24] We have not observed any analogous rearrangement with ammonia in the series of lactones described above.

2-Hydroxybutenolides and their methylated derivatives are uncommon as natural products. Vitamin C,

with hydroxy-groups at both the 2- and 3-positions, is widely distributed in nature and other 2-hydroxybutenolides are relatively common as artefacts produced during the processing of foods [25] and the pronounced flavour and odour of these compounds has led to their widespread use in the processed food industry. Sake develops a burnt taste on ageing due to the presence of 2-hydroxy-3,4-dimethyl-2-butenolactone (18).[26] It is suggested that this is produced by the condensation of 2-oxobutyric acid with acetaldehyde, both of which have been derived as acid degradation products of threonine. There is no suggestion that the lactone might be of microbial origin. Similarly, zymonic acid (19), which has been isolated from the culture solutions of several yeasts,[27] is now considered to be an artefact derived from pyruvic acid, since the compound can be produced when pyruvic acid (0.2—2.0%) is treated with calcium carbonate at room temperature for 2 d. We consider serpenone (2) to be a true metabolite of H. *serpens*.

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus, i.r. spectra on a Perkin-Elmer 681 spectrophotometer, u.v. spectra on a Unicam SP 800 spectrophotometer, ^{1}H n.m.r. spectra on a JEOL JNM–MH–100 spectrometer (with tetramethylsilane as an internal standard), and the mass spectra on an A.E.I. MS902 spectrometer. All thin layer (t.l.c.), preparative layer (p.l.c.), and column chromatography was done on Merck Kieselgel PF 256 + 366; preparative layers consisted of silica gel (16 g) on 20 × 20 cm glass plates.

Isolation of 3-Methoxy-4-methyl-5-prop-1-enylfuran-2(5H)-one (2) *and 3-Methoxy-4-methyl-5-propylfuran-2(5H)-one* (3).—*Hypoxylon serpens* (Barrons strain) was cultured in Thompson bottles (2 l) in a potato dextrose–yeast medium prepared from glucose (20 g), potatoes (200 g), yeast extract (Difco, 3 g), and water (1 l). After 8 weeks the brown solution was filtered off from the almost colourless mycelium, the filtrate (20 l) was extracted three times with diethyl ether, and the extract was dried (Na_2SO_4) and evaporated to yield a brown oil (2.3 g). This was dissolved in a mixture of light petroleum (b.p. 60—80 °C), diethyl ether, and acetic acid (70 : 30 : 3) (5 ml) and the solution applied to a column of silica gel (1.5 × 60 cm). Development of the column with the same solvent mixture gave a fraction which, on evaporation, yielded a pale yellow oil; this was distilled to yield the *furan-2(5H)-one* (2) (1.35 g) as an oil with a distinctive odour, b.p. 90—92 °C/1.5 mmHg (Found: C, 64.2; H, 7.2. $C_9H_{12}O_3$ requires C, 64.3; H, 7.1%); $\nu_{max.}$ 1 762 and 1 690 cm^{-1}; $\lambda_{max.}$ (EtOH) 227 nm (log ε 3.88). The lactone (2) (50 mg) was suspended in sodium hydroxide solution (3 ml; 2M) and the mixture set aside for 24 h. It was then acidified (H_2SO_4), and extracted three times with diethyl ether. Evaporation of the solvent from the combined extracts gave an oil which was separated (p.l.c.) in the above solvent system. Elution of the upper band and evaporation of the solvent gave the *furan-2(5H)-one* (3) (3 mg) with i.r. and mass spectra identical with the product obtained by catalytic hydrogenation of compound (2) described below.

Catalytic Reduction of the Furan-2(5H)-one (2).—A solution of the lactone (2) (0.5 g) in ethanol (50 ml) was reduced at atmospheric pressure in the presence of PtO_2 (0.1 g); 73 ml of hydrogen were absorbed. The solution was filtered and evaporated to yield an oil which was purified by chromatography on silica gel in the above solvent system to yield *3-methoxy-4-methyl-5-propylfuran-2(5H)-one* (3) as an oil (0.37 g) (Found: C, 63.75; H, 8.3. $C_9H_{14}O_3$ requires C, 63.5; H, 8.2%); $\nu_{max.}$ 1 762 and 1 692 cm^{-1}; M^+ 170.

Lithium Aluminium Hydride Reduction of the Furan-2(5H)-one (3).—To a solution of the lactone (3) (100 mg) in diethyl ether (20 ml) was added $LiAlH_4$ (20 mg), the mixture was stirred at room temperature for 1 h, and then the excess of hydride was destroyed by the addition of drops of ethyl acetate. The mixture was acidified (HCl; 1M), the diethyl ether layer was separated off, dried, and evaporated to yield crude *1-hydroxy-3-methylhept-3-en-2-one* (7) as an oil (77 mg); M^+ 142; δ($CDCl_3$) 0.96 (3 H, t), 1.26—1.76 (2 H, m), 1.86 (3 H, s), 2.26 (2 H, m), 3.8 (1 H, br, removed by D_2O), 4.58 (2 H, s), and 6.58 (1 H, t).

To the oil (7) was added acetic anhydride (1 ml) and pyridine (1 drop); the mixture was set aside at room temperature overnight and then poured into water. The resultant oil was extracted into diethyl ether. The diethyl ether layer was washed successively with dilute acid and water, and then dried and evaporated to yield *3-methyl-2-oxohept-3-enyl acetate* as an oil, *m/e* 184 (M^+), 142, 111, and 55; δ($CDCl_3$) 0.98 (3 H, t), 1.28—1.56 (2 H, m), 1.84 (3 H, s), 2.20 (3 H, s), 2.20 (2 H, m), 5.10 (2 H, s), and 6.60 (1 H, t).

1-Hydroxybut-2-enyl Cyanide.—To a stirred solution of but-2-enal (140 g) in diethyl ether (300 ml) at −10 °C was added a pre-cooled (−10 °C) solution of sodium cyanide (98 g) in water (250 ml) over 3—4 min and then a solution of HCl [36% HCl (200 ml) + water (200 ml)] as drops over 2 h at −10 °C. The mixture was then stirred at room temperature for 3 h after which the diethyl ether layer was separated, washed with water, dried, and evaporated to give a residual oil which was distilled to yield the cyanohydrin as an oil (107 g), b.p. 72 °C/1.5 mmHg (lit.,[16] b.p. 105—106 °C/13 mmHg).

1-Hydroxybutyl Cyanide.—n-Butyraldehyde (44 ml; 0.5 mol) was added to a cooled, freshly prepared solution of sodium hydrogensulphite (140 g in 70 ml of water), and the mixture was set aside overnight. It was then cooled to 0 °C, and aqueous potassium cyanide (33 g in 50 ml of water) added as drops over 1 h. The mixture was set aside for 1 h, then filtered, and the filtrate was extracted with diethyl ether. The diethyl ether extract was dried (Na_2SO_4), evaporated, and the residue distilled in the presence of sulphuric acid (1 drop) as stabiliser to yield butyraldehyde cyanohydrin (32 g), b.p. 103 °C/14 mmHg (lit.,[31] 103 °C/14 mmHg). The cyanohydrins of propionaldehyde, acetaldehyde, and benzaldehyde were prepared similarly.

1-(Tetrahydropyranyloxy)but-2-enyl Cyanide.—HCl (1 drop, 36%) was added to a mixture of 1-hydroxybut-2-enyl cyanide (48.5 g) and dihydropyran (42 g) which became warm and was set aside at room temperature overnight. The mixture was dissolved in diethyl ether, and the solution washed successively with aqueous sodium hydroxide (2M) and water, and then dried (Na_2SO_4) and evaporated. Distillation of the residual oil gave the *tetrahydropyranyl* ether (52 g), b.p. 90 °C/1.8 mmHg as an oil (Found: C, 66.3; H, 8.4; N, 7.6. $C_{10}H_{15}NO_2$ requires C, 66.3; H, 8.3; N, 7.7%).

Similarly prepared were *1-(tetrahydropyranyloxy)butyl cyanide* (from 1-hydroxybutyl cyanide), b.p. 89—90 °C/1.5 mmHg (Found: C, 65.3; H, 9.2; N, 7.5. $C_{10}H_{17}NO_2$ requires C, 65.6; H, 9.3; N, 7.65%); *1-(tetrahydropyranyl-*

oxy)ethyl cyanide (from 1-hydroxyethyl cyanide), b.p. 104 °C/25 mmHg (lit.,[32] b.p. 58—64 °C/0.35 mmHg); 1-(*tetrahydropyranyloxy)propyl cyanide* (from 1-hydroxypropyl cyanide), b.p. 72—74 °C/2.0 mmHg (Found: C, 63.8; H, 9.0; N, 8.3. $C_9H_{15}NO_2$ requires C, 63.9; H, 8.9; N, 8.3%); 2-(*tetrahydropyranyloxy)propan-2-yl cyanide* (from 2-hydroxypropan-2-yl cyanide), b.p. 106 °C/27 mmHg (Found: C, 63.9; H, 8.7; N, 8.1. $C_9H_{15}NO_2$ requires C, 63.9; H, 8.9; N, 8.3%); α-(*tetrahydropyranyloxy)benzyl cyanide* (from α-hydroxybenzyl cyanide), b.p. 133—134 °C/1.3 mmHg (Found: C, 71.8; H, 6.8; N, 6.4. $C_{13}H_{15}NO_2$ requires C, 71.9; H, 6.9; N, 6.45%).

4-*Hydroxy*-3-*methyl*-5-(*prop*-1-*enyl*)*furan*-2(5H)-*one* (8).—A mixture of clean zinc wool (29.1 g; 0.45 mol), 1-(tetrahydropyranyloxy)but-2-enyl cyanide (54.3 g; 0.3 mol), ethyl 2-bromopropioniate (81.45 g; 0.45 mol), and copper(II) bromide (0.2 g) in benzene (500 ml) was heated under reflux for 1 h. The mixture developed a yellow-green colouration as the zinc dissolved. The solution was cooled to 0 °C and sulphuric acid (300 ml, 20%) was added as drops to the stirred solution over 30 min, after which it was stirred at room temperature for a further 3 h. It was then set aside at room temperature overnight. Three layers were formed: a lower aqueous layer, a gummy interface layer, and an upper benzene layer. The lower acid layer was separated off and the upper gummy and benzene layers were together dissolved in diethyl ether (200 ml) and shaken vigorously with aqueous sodium hydroxide. The lower aqueous layer was separated off, washed once with diethyl ether (100 ml), and acidified with hydrochloric acid (36%). Diethyl ether extraction (3 × 100 ml) and evaporation of the dried diethyl ether extract gave an amber coloured oil which partially solidified when cooled. The acid layer from the initial separation was extracted twice with diethyl ether, washed with water, dried, and evaporated to give more gummy solid. The combined gummy solids were triturated with acetonitrile (10 ml) and the mixture cooled to 0 °C overnight. Filtration gave a granular solid which was recrystallised from a small volume of acetonitrile at 0 °C and then from water to yield the *furan*-2(5H)-*one* (8) (6.2 g), m.p. 124—125 °C as needles and plates (Found: C, 62.1; H, 6.6. $C_8H_{10}O_3$ requires C, 62.1; H, 6.5%); $\nu_{max.}$($CHCl_3$) 3 400—2 400, 1 742, and 1 669 cm^{-1}; δ($CDCl_3$) 1.75 (3 H, d, *J* 7 Hz), 1.77 (3 H, s), 5.06—5.47 (2 H, m), 6.01 (1 H, m), and 10.15 (1 H, br, removed by D_2O).

Similarly prepared were 4-*hydroxy*-3-*methyl*-5-*phenylfuran*-2(5H)-*one* (10.9 g) [from α-(tetrahydropyranyloxy)benzyl cyanide (0.2 mol)] as needles from acetonitrile and then water, m.p. 145—146 °C (Found: C, 69.3; H, 5.2. $C_{11}H_{10}O_3$ requires C, 69.5; H, 5.3%); 4-hydroxy-3,5,5-trimethylfuran-2(5H)-one (3.2 g) [from 2-(tetrahydropyranyloxy)-propan-2-yl cyanide (0.2 mol)] as needles from acetonitrile and then water, m.p. 211—212 °C (lit.,[28] 135—139 °C) (Found: C, 58.8; H, 7.3. $C_7H_{10}O_3$ requires C, 59.15; H, 7.0%); δ[$(CD_3)_2C{=}O$] 1.42 (6 H, s), and 1.57 (3 H, s); 4-hydroxy-3,5-dimethylfuran-2(5*H*)-one (3.1 g) [from 1-(tetrahydropyranyloxy)ethyl cyanide (0.1 mol)] as needles from acetonitrile and then water, m.p. 125 °C (lit.,[29] 121—122.5 °C) (Found: C, 49.5; H, 6.6. Calc. for $C_6H_8O_3{\cdot}H_2O$: C, 49.3; H, 6.8%); 5-*ethyl*-4-*hydroxy*-3-*methylfuran*-2(5H)-*one* (3.3 g) [from 1-(tetrahydropyranyloxy)propyl cyanide (0.1 mol)] as needles from acetonitrile and then water, m.p. 87 °C (Found: C, 59.0; H, 7.15. $C_7H_{10}O_3$ requires C, 59.1; H, 7.0%); 4-*hydroxy*-3-*methyl*-5-*propylfuran*-2(5H)-*one* (3.8 g) [from 1-(tetrahydropyranyloxy)butyl cyanide (0.1 mol)] as needles from acetonitrile and then water, m.p. 93—95 °C (Found: C, 61.8; H, 7.7. $C_8H_{12}O_3$ requires C, 61.5; H, 7.7%); 3-*ethyl*-4-*hydroxy*-5-*propylfuran*-2(5H)-*one* (3.2 g) [from 1-(tetrahydropyranyloxy)butyl cyanide (0.1 mol) and ethyl 2-bromobutyrate (0.15 mol)] as needles from acetonitrile (with much loss) and then aqueous alcohol, m.p. 61—62 °C (Found: C, 63.3; H, 8.1. $C_9H_{14}O_3$ requires C, 63.5; H, 8.2%).

4-*Methoxy*-3-*methyl*-5-(*prop*-1-*enyl*)*furan*-2(5H)-*one* (4).—Dimethyl sulphate (2.52 g) was added over 30 min to a mixture of the tetronic acid (3.08 g) and anhydrous potassium carbonate (2.8 g) in acetone (20 ml). The mixture was refluxed for 6 h, then filtered, and the filtrate was evaporated off and the residue distilled to yield an oil (3.0 g), b.p. 106—108 °C/0.1 mmHg which slowly solidified. Recrystallisation from light petroleum gave long needles of the *furan*-2(5H)-*one* (4), m.p. 44—45 °C (Found: C, 64.0; H, 7.2. $C_9H_{10}O_3$ requires C, 64.3; H, 7.1%); $\nu_{max.}$ ($CHCl_3$) 1 752 and 1 670 cm^{-1}; δ($CDCl_3$) 1.76 (3 H, dd, *J* 7 and 1.5 Hz), 1.87 (3 H, d, *J* 1.5 Hz), 4.03 (3 H, s), 5.05—5.4 (2 H, m), 5.94 (1 H, dq, *J* 7 and 16 Hz).

Similarly prepared was 4-*methoxy*-3-*methyl*-5-*propylfuran*-2(5H)-*one* (5) as an oil, b.p. 89—92 °C/1.5 mmHg (Found: C, 63.3; H, 8.3. $C_9H_{14}O_3$ requires C, 63.5; H, 8.2%); δ($CDCl_3$) 0.96 (3 H, t, *Me*CH_2), 1.40 (4 H, m, MeCH_2CH_2), 1.92 (3 H, s, C=CMe), 4.14 (3 H, s, OMe), and 4.64 (1 H, t, CH_2CHO).

Ethyl 2-*Methyl*-3-*oxoheptanoate*.—A mixture of 1-cyanobutane (24.9 g; 0.3 mol) and ethyl 2-bromopropionate (81.5 g; 0.45 mol) was added over 15 min to a suspension of zinc wool (29.25 g) in dry benzene (400 ml). The mixture turned a greenish colour during the addition. The mixture was refluxed for 45 min, then cooled to 0 °C, and ice-cold sulphuric acid (300 ml; 12N) was added to the stirred solution, which was then stirred for a further 45 min at room temperature. The two phases were separated to give an aqueous phase which was diluted and then re-extracted with benzene (100 ml). The combined benzene layers were washed successively with water, saturated sodium hydrogencarbonate solution, and water, and then dried (Na_2SO_4). Evaporation and distillation of the residue gave the required heptanoate (21.2 g), b.p. 112—124 °C/10 mmHg as an oil.

Ethyl 2-*Bromo*-2-*methyl*-3-*oxoheptanoate*.—Bromine (16 g) was added as drops to a stirred mixture of the above ester (17.2 g) and crushed ice (40 g) over 30 min. The mixture was extracted with diethyl ether (3 × 50 ml), the diethyl ether solution was washed three times with water, dried (Na_2SO_4), evaporated, and the residual oil distilled to yield the required *heptanoate* (19.5 g) as a pale yellow oil, b.p. 82.86 °C/1 mmHg.

4-*Hydroxy*-3-*methyl*-5-*propylfuran*-2(5H)-*one* (20) *obtained from Ethyl* 2-*Bromo*-2-*methyl*-3-*oxoheptanoate*.—A mixture of the bromo-ester (10 g) and HBr (1 drop, *d*, 1.46) was heated on a water-bath for 12 h. The resulting brown oil solidified on cooling. The solid was extracted twice with boiling water and the combined extracts, after filtration in the presence of a little charcoal, was set aside. The solid which deposited was filtered off and recrystallised from water to yield the required tetronic acid as needles (4.1 g), m.p. 93—95 °C, identical by mixed m.p. and i.r., ^1H n.m.r., and mass spectroscopy, with the product prepared by the cyanohydrin synthesis.

3-*Hydroxy*-4-*methyl*-5-*propylfuran*-2(5H)-*one* (9).—A mixture of anhydrous pyridine (75 ml), ethyl ethoxalylpropionate (37 g), and butyraldehyde (30 ml) was set aside

at room temperature for 4 d and then evaporated at 65 °C under reduced pressure (rotary evaporator) to remove the bulk of the pyridine. To the oily residue was added acetic acid (50 ml), concentrated hydrochloric acid (50 ml), and water (50 ml) and the mixture was refluxed for 8 h. The solution was then evaporated at 65 °C (rotary evaporator) to remove the volatiles and the sticky brown residue was dissolved in ethyl acetate (150 ml). The ethyl acetate solution was washed with saturated sodium chloride solution (3 × 50 ml), dried (Na_2SO_4), and evaporated to yield a dark brown oil, distillation (×2) of which gave the *furan*-2(5H)-*one* (9) as a viscous, pale yellow oil (12.5 g), b.p. 101—104 °C/0.1 mmHg (lit.,[21] b.p. 96 °C/0.004 mmHg; lit.,[20] b.p. 87—90 °C/0.08 mmHg) (Found: C, 61.8; H, 7.7. Calc. for $C_8H_{12}O_3$: C, 61.5; H, 7.7%); $\nu_{max.}$($CDCl_3$) 3 520s, 3 350, 2 600, 1 755, and 1 715 cm^{-1}; δ($CDCl_3$) 0.96 (3 H, s), 1.44 (4 H, m), 1.92 (3 H, d, *J* 3 Hz), 4.76 (1 H, t), and 7.44 (1 H, s, exchanged by D_2O).

3-*Methoxy*-4-*methyl*-5-*propylfuran*-2(5H)-*one* (3).—The 3-hydroxy-lactone (9) (3 g) in diethyl ether was treated with an excess of ethereal diazomethane. After 30 min, the excess of diazomethane was destroyed (AcOH) and the diethyl ether was evaporated. Distillation of the residual oil gave the *furan*-2(5H)-*one* (3) as an oil, b.p. 106 °C/2.5 mmHg (1.7 g) of distinctive odour, identical with the product obtained from the catalytic reduction of the natural product (2) (Found: C, 63.65; H, 8.5. $C_9H_{14}O_3$ requires C, 63.5; H, 8.2%).

5-(2-*Chloropropyl*)-3-*hydroxy*-4-*methylfuran*-2(5H)-*one* (11).—3-Chlorobutanal [21] was prepared by passing dry HCl through an ice-cooled solution of crotonaldehyde (100 g), dissolved in diethyl ether (150 ml), for 1.25 h and the diethyl ether was then removed at room temperature on a rotary evaporator. The crude 3-chlorobutanal was used without further purification. 3-Chlorobutanal (37.1 g; 0.35 mol) was added as drops over 30 min to a mixture of ethyl ethoxalylpropionate (50.5 g; 0.25 mol) and pyridine (50 ml), cooled to 0 °C, and the resultant mixture was set aside for 4 d at room temperature. The clear, orange solution was evaporated to remove the pyridine and the residual oil was refluxed for 8 h with a mixture of HCl (50 ml, 36%), water (50 ml), and acetic acid (50 ml) during which the orange solution rapidly turned brown and a brown oil appeared on the surface of the solution. The solvent was evaporated off at 65 °C (rotary evaporator) and the residual gum was dissolved in ethyl acetate (150 ml). The ethyl acetate solution was washed with saturated sodium chloride solution (2 × 50 ml), dried, and evaporated. The dark brown, viscous gum was distilled to yield a pale yellow viscous oil, b.p. 120—140 °C/0.3 mmHg which solidified over 24 h to yield a waxy yellow solid (11.2 g). Recrystallisation of this three times from light petroleum and then water yielded needles and plates of the *furan*-2-(5H)-*one* (11), m.p. 93—94 °C; $\nu_{max.}$($CHCl_3$) 3 520s, 3 400—2 700, 1 755, and 1 705 cm^{-1}; δ($CDCl_3$) 1.6 (3 H, d, *J* 7 Hz) and 1.62 (3 H, d, *J* 7 Hz), which indicates a mixture of two isomers.

5-(2-*Chloropropyl*)-3-*methoxy*-4-*methylfuran*-2(5H)-*one* (12).—A solution of the crude hydroxy-lactone (11) (9 g) was treated with an excess of ethereal diazomethane. After 2 h, the diethyl ether was removed and the residual oil was distilled to yield the ether (12) as a viscous oil (5.2 g), b.p. 107—108 °C/0.3 mmHg which slowly solidified to yield a pale yellow solid. Column chromatography on silica gel in the solvent system light petroleum (b.p. 60—80 °C)–diethyl ether–acetic acid (70 : 30 : 3) gave two closely spaced components. The upper component crystallised from light petroleum (b.p. 60—80 °C) to yield needles, m.p. 49—50 °C, of the *furan*-2(5H)-*one* (12); $\nu_{max.}$ 1 758, 1 682, and 1 012s cm^{-1} (Found: C, 52.8; H, 6.6; Cl, 17.6. $C_9H_{13}ClO_3$ requires C, 52.8; H, 6.3; Cl, 17.3%). The compound became oily over 14 d at room temperature, but was stable at 0 °C over an extended period. The lower component from the column was obtained as a pale yellow oil; $\nu_{max.}$ ($CHCl_3$) 1 758 and 1 682 cm^{-1} (Found: C, 52.7; H, 6.5; Cl, 17.4. $C_9H_{13}ClO_3$ requires C, 52.8; H, 6.3; Cl, 17.3%.)

3-*Methoxy*-4-*methyl*-5-*propylidenefuran*-2(5H)-*one* (13).—A mixture of the freshly distilled chloro-compound (12) (1 g) and DBN (2 g) in dry benzene (25 ml) was refluxed for 48 h. The solvent was removed under reduced pressure, hydrochloric acid (10 ml, 2M) was added to the residual oil, and the mixture was extracted with ethyl acetate (2 × 10 ml). The ethyl acetate extract was washed with saturated sodium chloride solution (10 ml), dried, and evaporated to give a brown oil, p.l.c. of which [light petroleum (b.p. 60—80 °C)–diethyl ether–acetic acid (70 : 30 : 3)] gave 2 bands. The upper band gave an oil which slowly deposited a small quantity of solid and both oil and solid were dissolved in light petroleum, cooled to 0 °C, and filtered to give methoxymethylmaleic anhydride as plates (14 mg), m.p. and mixed m.p. (with an authentic sample) 44 °C;[30] δ($CDCl_3$) 2.06 (3 H, s), and 4.25 (3 H, s); $\nu_{max.}$(KBr) 1 876, 1 775, and 1 675 cm^{-1}.

The light petroleum filtrate was evaporated to yield the 5-*propylidenefuran*-2(5H)-*one* (13) (80 mg) as an oil (Found: C, 64.1; H, 7.0. $C_9H_{12}O_3$ requires C, 64.3; H, 7.1%); δ($CDCl_3$) 1.06 (3 H, t), 1.96 (3 H, s), 2.34 (2 H, m), 4.00 (3 H, s), and 5.04 (1 H, t).

The lower band from the separation gave unchanged chloro-lactone (364 mg).

Isomerisation of the Natural Lactone (2).—A mixture of the lactone (2) (250 mg), DBN (500 mg), and benzene was refluxed 24 h. After cooling the solvent the residue was worked-up and separated, as described above, to yield methoxymethylmaleic anhydride (4 mg) and 5-*propylidene*-*furan*-2(5H)-*one* (13) (90 mg).

3-*Methyl*-4-*methoxy*-5-*propylidenefuran*-2(5H)-*one* (15) *and* 4-*Hydroxy*-3-*methyl*-5-*propylidenefuran*-2(5H)-*one* (14).—A mixture of the furan-2(5*H*)-one (4) (0.3 g), DBN (1 g), and toluene (5 ml) was heated on a water-bath overnight to give a brown mixture which was evaporated under reduced pressure to remove toluene. The residue was dissolved in diethyl ether and the diethyl ether solution was washed with sulphuric acid (2M; 2 × 5 ml), after which it was washed, dried, and evaporated to yield a pale yellow oil. T.l.c. [light petroleum–diethyl ether–acetic acid (70 : 30 : 3)] showed the presence of two components (iodine spray). Separation by p.l.c. gave, from the upper band, (*Z*)-3-*methyl*-4-*methoxy*-5-*propylidenefuran*-2(5H)-*one* (15) (203 mg) as an oil; $\nu_{max.}$($CHCl_3$) 1 747, 1 662, and 1 658 cm^{-1}; δ($CDCl_3$) 1.06 (3 H, t), 2.03 (3 H, t), 2.24 (2 H, m), 4.1 (3 H, s), and 5.23 (1 H, t) (Found: C, 64.1; H, 6.9. $C_9H_{12}O_3$ requires C, 64.3; H, 7.1%).

The lower band gave the *furan*-2(5H)-*one* (14) (50 mg) as needles (from water and then toluene), m.p. 114—115 °C; $\nu_{max.}$ 3 600—2 500, 1 730s, 1 690w, and 1 642vs cm^{-1}; δ[$(CD_3)_2CO$] 1.78 (3 H, s), 1.08 (3 H, t), 2.31 (2 H, m), 5.47 (1 H, t), and 9.6—7.8 (1 H, removed by D_2O) (Found: C, 62.3; H, 6.4. $C_8H_{10}O_3$ requires C, 62.1; H, 6.5%).

Similar treatment of the furan-2-(5*H*)-one (8) with DBN (400 mg) in benzene (5 ml) over 48 h gave, after acidification,

extraction with ethyl acetate, and p.l.c. of the residue in the above solvent system, (Z)-3-*methyl*-4-*hydroxy*-5-*propylidene*-*furan*-2(5H)-*one* (14) (75 mg) as needles (after recrystallisation from water and toluene), m.p. 114—115 °C, identical with compound described above.

(Z)- *and* (E)-3-*Methyl*-4-*methoxy*-5-*propylidenefuran*-2(5H)-*one* (15).—A solution of 3-methoxy-4-methyl-5(2*H*)-oxofuran-2-yltriphenylphosphonium bromide in dimethyl sulphoxide (DMSO) (10 ml) was added to a stirred solution of the anion, derived from a mixture of sodium hydride (0.96 g, 50%, in oil) and dry DMSO (40 ml) which was stirred at 65—70 °C for 1 h. To the red-brown solution was added propanal (2.32 g) and the mixture was stirred at room temperature for 3 d. The mixture was poured into iced water and the solution acidified and extracted with diethyl ether. The mixture was dried (Na_2SO_4), the solvent evaporated off, and the residual gum separated (p.l.c.) using chloroform to yield two closely running fractions. The faster-running fraction gave the (*Z*)-5-*propylidenefuran*-2(5H)-*one* (15) (52 mg) as an oil; δ($CDCl_3$) 1.06, (3 H, t), 2.03 (3 H, s), 2.24 (2 H, m), 4.1 (3 H, s), and 5.23 (1 H, t), identical with the sample produced by rearrangement of the prop-1-enyl lactone. The slower-running fraction gave the (E)-*isomer* as an oil (28 mg); δ($CDCl_3$) 1.06 (3 H, t), 2.08 (3 H, s), 2.39 (2 H, m), 4.15 (3 H, s), and 5.48 (1 H, t).

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