Studies related to Cyclopentanoid Natural Products. Part 1. Preparation of (4*RS*)- and (4*R*)-4-Hydroxy-2-hydroxymethylcyclopent-2-en-1-one; a Versatile Synthetic Intermediate[1]

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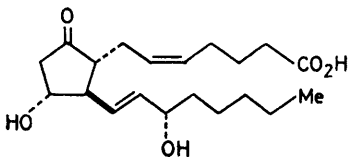
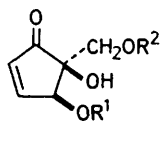
The racemate of 2,5-dihydro-3-hydroxymethyl-2,5-dimethoxy-2-methylfuran (11), prepared from the reaction of 3-hydroxymethyl-2-methylfuran (12b), with bromine in methanol, is converted into the racemate of 4-hydroxy-2-hydroxymethylcyclopent-2-en-1-one (9a) when heated in aqueous dioxan buffered at pH 6.3.

Methyl quinate (17b), obtained by treating D-(−)-quinic acid (17a) with methanolic hydrogen chloride, reacts with ammonia in methanol to give quinamide (17c) which affords 1,1′-*ON*-isopropylidene-3,4-*O*-isopropylidene-quinamide (27a) in the presence of acetone containing hydrogen chloride. Benzoyl chloride in pyridine transforms compound (27a) into the 5-*O*-benzoate (27b) which undergoes selective hydrolysis in hot aqueous acetic acid to give 5-*O*-benzoyl-1,1′-*ON*-isopropylidenequinamide (26). Sequential treatment of compound (26) with sodium periodate in aqueous tetrahydrofuran (THF) and pyrrolidinium acetate in hot benzene affords (5*R*,8*R*)-8-benzoyloxy-2,2-dimethyl-4-oxo-1-oxa-3-azaspiro[4.4]non-6-ene-6-carbaldehyde (32). The aldehyde (32) is transformed into (5*R*,8*R*)-8-hydroxy-6-hydroxymethyl-2,2-dimethyl-1-oxa-3-azaspiro[4.4]non-6-en-4-one (34a) by reaction with sodium borohydride in THF followed by methanolic sodium methoxide. Hydrazinolysis of the oxazolidinone ring of the last-described compound is effected in boiling hydrazine hydrate to yield (1*R*,4*R*)-1,4-dihydroxy-2-hydroxymethylcyclopent-2-ene-1-carbohydrazide (35a). Treatment of the acid hydrazide (35a) with nitrous acid and thermolysis of the derived acid azide (35b) gives (4*R*)-4-hydroxy-2-hydroxymethylcyclopent-2-en-1-one (9a).

A WIDE range of biological properties are associated with several relatively simple compounds incorporating the cyclopentanone unit. For example, the prostaglandins, of which protaglandin E_2 (1) is a familiar example, exert diverse physiological effects upon the mammalian respiratory, digestive, renal, reproductive, cardiovascular, endocrine, and nervous systems.[2] The pentenomycins (2a)—(2c),[3] dehydropentenomycin (3),[4] xanthocidin (4),[5] and vertimycin (5)[6] display antibacterial activity. Cryptosporiopsin (6) is active against fungi,[7] and methylenomycin A (7)[8] and sarkomycin (8)[9] possess antitumour properties.

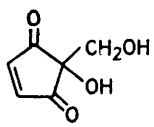


(1)



(2)

a; $R^1 = R^2 = H$
b; $R^1 = Ac, R^2 = H$
c; $R^1 = H, R^2 = Ac$



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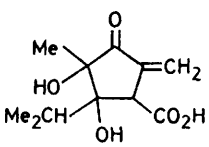

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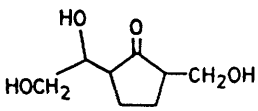

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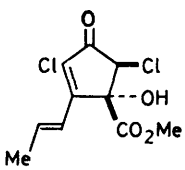

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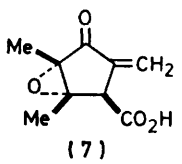

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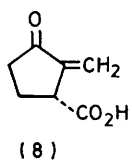


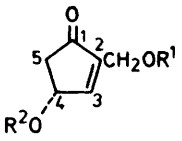
(8)

As part of a programme to define structure–activity relationships of compounds of the foregoing type, we have initiated a synthetic study of functionally substituted cyclopentanones. In considering routes to prostanoids, we were impressed by the potential of cyclopentenones of type (9), particularly if such compounds were available in an optically pure form. Furthermore, such compounds were also expected to serve as precursors of the pentenomycins (2a)—(2c) and their analogues, of dehydropentenomycin (3) and its analogues, and of analogues of vertimycin (5), methyleneomycin A (7), and sarkomycin (8). We now describe the synthesis of the compound (9a), both as the racemate and the (4*R*)-isomer.

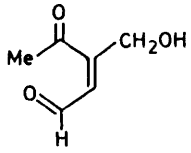
RESULTS AND DISCUSSION

The synthesis of the racemate of the cyclopentenone (9a) relied upon achieving the intramolecular aldol reaction of the species (10); this approach defined the racemate of the dihydrofuran (11) as a possible precursor. Treatment of the furan (12b)[10] [obtained by the lithium aluminium hydride reduction of the furan (12a), itself prepared from ethyl acetoacetate and chloroacetaldehyde] in methanol–ether at −78 °C with bromine (1 mol equiv.) followed by triethylamine (2.5 mol equiv.) gave the racemate of the dihydrofuran (11) (80%), as a mixture of diastereoisomers. An attempt to convert

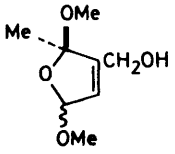
compound (11) into the target system (9a), by using Amberlite IR 120 (H^+) ion-exchange resin followed by sodium carbonate, according to the procedure of Lee,[11] was unrewarding. However, the desired reaction was achieved in refluxing aqueous dioxan buffered at pH 6.3,



(9)
a; $R^1 = R^2 = H$



(10)



(11)

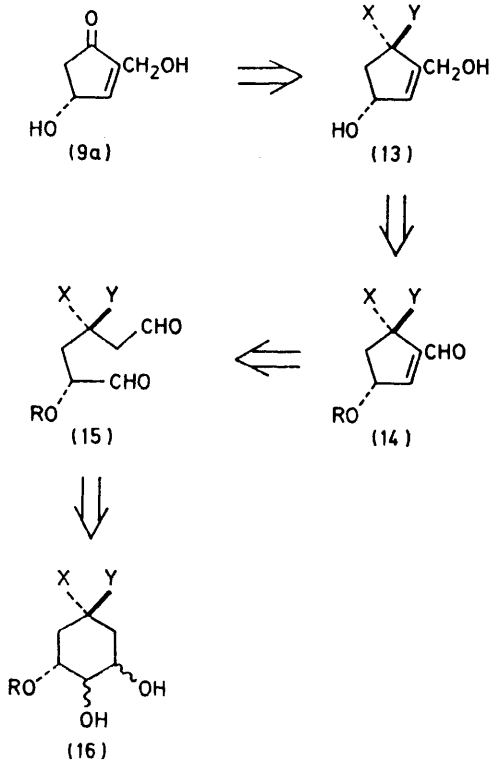
(12)
a; $R = CO_2Et$
b; $R = CH_2OH$

by the method of Floyd;[12] after silica-gel chromatography, the racemate of the cyclopentenone (9a) was isolated in 50% yield.

The structure of compound (9a) was deduced from its elemental composition and its spectroscopic properties. In particular, the ^1H n.m.r. spectrum (CD_3COCD_3) showed signals at δ 2.20 and 2.80 (for the ring methylene protons), at 4.88 (for the saturated methine proton), and at 7.35 (for the vinylic methine proton); the ring methylene protons were coupled to each other (J 16 Hz) and to the saturated methine proton (J 3 and 6 Hz) which, in turn, was coupled to the vinylic methine proton (J 2 Hz). In accord with the presence of the enone function, compound (9a) absorbed in the u.v. region at 224 nm (ε 7 800) and in the i.r. region at 1 700 and 1 645 cm^{-1}.

Our retrosynthetic analysis for the construction of the optically active cyclopentenone (9a) is outlined in the Scheme. The key step in the planned sequence rested upon achieving the intramolecular aldolisation and dehydration of a species of type (15); this approach defined a cyclohexane of type (16) as a sub-target. Whilst there has long been precedent for such oxidative ring-contractions,[13-17] it was vital, in the present context, that the intermediate dialdehyde (15) should suffer no epimerisation at the oxygenated chiral centre. The requirements of the groups X, Y, and R deserve comment. Clearly, X and Y should be readily elaborated and they should be stable to the conditions of the oxidative ring-contraction; furthermore, since the target (9a) may be expected to possess limited optical stability to acids and bases, the groups should be convertible into the oxo-moiety under essentially neutral conditions. The alcohol-protecting group R must also be both readily introduced and capable of withstanding the conditions of the oxidative ring-contraction; finally, were the compound (14) to undergo a reductive cleavage in the presence of metal hydrides, it should be possible to effect the removal of R in tandem with the aldehyde reduction.

The choice of D-(−)-quinic acid (17a) as the starting material for the generation of a cyclohexane of type (16) was dictated by three considerations. Quinic acid is readily available commercially in optically pure form. It incorporates functionality at C-1, which may be



X,Y = masked carbonyl group

SCHEME

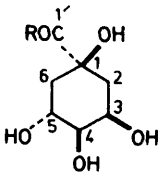
regarded as a masked carbonyl group. Finally, it possesses the correct absolute stereochemistry at *both* C-3 and -5. Clearly, therefore, the sub-target (16) can be refined to a cyclohexane of type (18) or (19) and the initial problem involves the derivation of such compounds from quinic acid (17a).

Quinide (20a), which is readily formed by heating quinic acid (17a),[18] appeared to be an ideal candidate to test the foregoing speculations. If its oxidative ring-contraction could be effected, the derived cyclopentene (21a) should be convertible into the target (9a) by sequential reaction with sodium borohydride and sodium periodate.

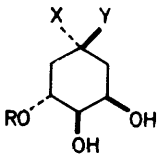
Quinide (20a), prepared (55% after sublimation) by a slight modification of the literature method,[18] was oxidatively cleaved with sodium periodate, but attempts to convert the oxidation product into the cyclopentene

(21a), in the presence of sodium hydroxide–ether,[14] aqueous sodium carbonate–tetrahydrofuran (THF),[11] and refluxing aqueous dioxan buffered at pH 6.3,[12] were without avail.

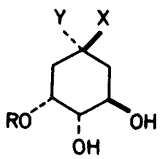
In many of the established ring contractions of cyclohexanediols to cyclopentenecarbaldehydes, the aldolisation step is conducted in the presence of piperidinium [15]



(17)



(18)
a; R = OH
b; R = OMe
c; R = NH_2



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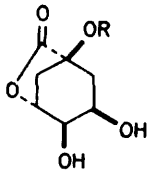

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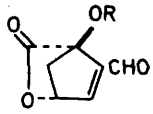
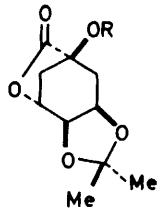


(21)
a; R = H
b; R = CO_2Et

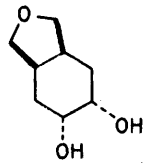


(22)

or pyrrolidinium acetate,[19] and usually in a relatively non-polar solvent, such as benzene. The solubility characteristics of the periodate-oxidation product of quinide (20a) precluded an examination of its behaviour under such conditions.

In the hope of overcoming the aforementioned difficulty, it was decided to attempt the aldolisation of the periodate-oxidation product of the ethoxycarbonyl quinide (20b). Using a slight modification of the literature procedure,[20] quinic acid (17a) was converted (72%) into the isopropylidene derivative (22a) in the presence of acidic acetone. When treated with ethyl chloroformate in pyridine, according to the published method,[21] compound (22a) afforded (98%) the ethoxycarbonyl derivative (22b) which was quantitatively transformed into the diol (20b) by hot aqueous acetic acid. Unfortunately, the product of oxidation of the diol (20b) with sodium periodate gave a complex mixture of products when heated with piperidinium acetate in benzene; there was no evidence for the presence of an aldehydic signal in the n.m.r. spectrum of the mixture. It has been reported that the diol (23), on treatment with lead(IV) acetate in acetic acid followed by sodium carbonate, affords the cyclopentenecarbaldehyde (24); [17] however, a complex mixture of products, which lacked an aldehyde signal in the n.m.r. spectrum, resulted when compound (20b) was similarly treated.

Possibly, the failure to bring about the oxidative ring-contraction of the diols (20a) and (20b) to the cyclopentenes (21a) and (21b) may be ascribed to the substantial strain energy engendered in the products. In consequence, the presumed intermediates (25a) and (25b) may undergo other reactions, *e.g.* β-eliminations. In the hope of overcoming such problems, the isopropylidenequinamide (26) was next selected for study. In their work defining the structure of quinic acid, Fischer and Dangschat [22] had prepared the di-isopropylidenequinamide (27a); furthermore, they had shown that the dioxolan ring of compound (27a) could be selectively cleaved under hydrolytic conditions.



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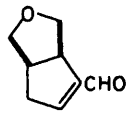

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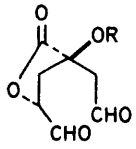
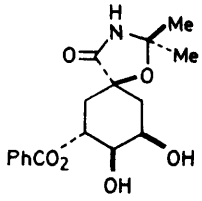
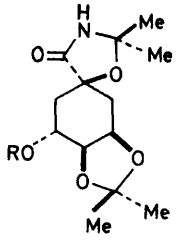


(25)
a; R = H
b; R = CO_2Et



(26)

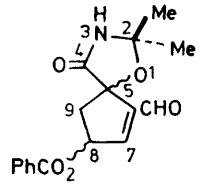


(27)
a; R = H
b; R = COPh

Methyl quinate (17b), prepared in quantitative yield by heating quinic acid (17a) in methanolic hydrogen chloride, was converted (74%) into quinamide (17c) in the presence of methanolic ammonia. Reaction of quinamide (17c) with acetone–hydrogen chloride, as described by Fischer and Dangschat,[22] gave a mixture of products which was separated by silica-gel chromatography to give the isopropylidenequinide (22a) (14%) and the desired di-isopropylidenequinamide (27a) (38%). Treatment of compound (27a) with benzoyl chloride in pyridine afforded (86%) the benzoate (27b) which was hydrolysed by hot aqueous acetic acid to give the diol (26) (81%).

Oxidation of the diol (26) with sodium periodate and treatment of the oxidation product with pyrrolidinium acetate in hot benzene gave the cyclopentenecarbaldehyde (28) in 67% yield (after SiO_2 chromatography). The constitution of the compound (28) was established by analytical and spectroscopic evidence. In particular, the ^1H n.m.r. spectrum ($CDCl_3$) showed signals at δ 2.60 and 2.80 (for the methylene protons), at 6.32 (for the saturated methine proton), at 7.16 (for the vinylic methine proton), and at 9.85 (for the aldehydic proton); the ring protons were coupled to each other (J 14.5 Hz) and to the saturated methine proton (J 6 and 7 Hz) which, in turn, was further coupled to the vinylic methine proton (J 2 Hz).

Compound (28) was clearly a single diastereoisomer on



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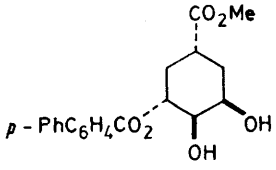

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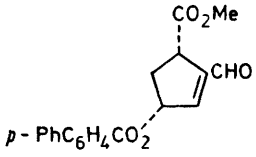
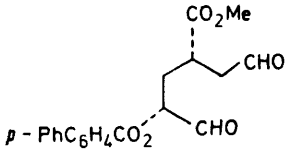


(30)



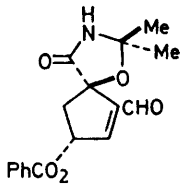
(31)

the basis of its ^1H and ^{13}C n.m.r. spectra, its sharp melting point, and its homogeneity on t.l.c. Furthermore, an examination of the crude product (t.l.c. and ^1H n.m.r. spectroscopy) failed to provide any evidence for the presence of the other diastereoisomer. Since compound (28) was optically active {$[\alpha]_D$ +87° (EtOH)}, it is likely to be enantiomerically pure.

Recently, Trost and his co-workers [23] have reported the oxidative ring-contraction of the diol (29) into the cyclopentenecarbaldehyde (30), using conditions similar to those described in this study; no epimerisation at the oxygenated chiral carbon of the intermediate dialdehyde (31) was detected. Accordingly, we infer that compound (28) is probably the stereoisomer (32) although the structure (33) cannot be excluded.

Having achieved our sub-target, attention was turned to the conversion of the cyclopentenecarbaldehyde (32) into the target (9a). When treated with lithium borohydride in THF, compound (32) was converted into the diol (34a) (31% after SiO_2 chromatography). An attempt to improve the yield, by employing lithium aluminium hydride, was unsuccessful. However, by adopting a two-step procedure, involving reduction with sodium borohydride in THF to give the alcohol (34b) followed by methanolysis with methanolic sodium methoxide, compound (34a) was isolated in 80% yield (after SiO_2 chromatography).

The carbonyl group of the oxazolidinone ring of compound (34a) was surprisingly unreactive to nucleophilic attack. For example, no reaction occurred over a 2 h period in the presence of boiling 2M-potassium hydroxide. However, in boiling hydrazine hydrate, the acid hydrazide (35a) was obtained (80% after SiO_2 chromatography). Treatment of the compound (35a) with nitrous acid at 0 °C gave the acid azide (35b) which, without purification, was heated in water. Following silica-gel chromatography of the product, the cyclopentenecarbinol (9a) was isolated [42% based upon (35a)]. Although its



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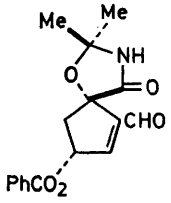

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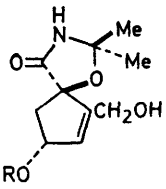
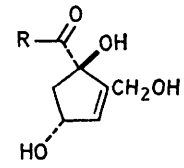
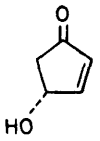


(34)
a; R = H
b; R = COPh



(35)
a; R = $NHNH_2$
b; $R = N_3$



(36)

spectroscopic properties were indistinguishable from those of the material prepared from the furan (12a), compound (9a) was optically active {$[\alpha]_D$ +50° (EtOH)}. This value is similar in sign, but less in magnitude, to that of the structurally related compound (36) [24] {$[\alpha]_D$ +81° ($CHCl_3$)}, a result which further supports the assignment of the *R*-configuration to the 8-oxy-substituent of compound (28).

In summary, 4-hydroxy-2-hydroxymethylcyclopent-2-en-1-one has been prepared as the racemate and as the (4*R*)-isomer. The former synthesis, which used ethyl acetoacetate and chloroacetaldehyde diethyl acetal as starting materials, involved a five-step sequence and proceeded in 14% overall yield. The latter synthesis, which commenced with quinic acid (17a), required ten steps and afforded the product in 3.5% overall yield.

EXPERIMENTAL

Tetrahydrofuran (THF) was dried over calcium hydride and, immediately prior to use, was distilled. Acetone was

dried over calcium chloride and distilled. Pyridine was dried over potassium hydroxide, distilled, and stored over molecular sieves (Type 4A). Triethylamine was stored over sodium hydroxide. Methanol was dried by means of magnesium activated with iodine and distilled. All other solvents and chemicals were employed as purchased.

T.l.c. was performed on Scheicher and Schull plastic sheets coated with silica gel (F 1500 LS254); the plates were initially examined under u.v. light and then developed with either iodine vapour or an aqueous potassium permanganate spray. Column chromatography was effected, under pressure, using Merck Kieselgel H (Type 60).

Evaporations were carried out at *ca.* 40 °C using a Buchi rotary evaporator. M.p.s were determined using a Kofler hot-stage apparatus and were uncorrected. A Bendix–Ericson automatic polarimeter was used to measure optical rotations. I.r. spectra were recorded using a Hilger and Watts Infrascan. A Unicam SP 800 spectrometer was employed to determine u.v. spectra. N.m.r. spectra refer to tetramethylsilane or sodium 3-trimethylsilylpropane-1-sulphonate as internal standards; ^{1}H n.m.r. spectra were measured at 60 MHz using a Varian EM 360 spectrometer and ^{13}C n.m.r. spectra were recorded at 20 MHz with a Varian CFT-20 spectrometer. Mass spectra were determined using an A.E.I. MS9 spectrometer operating at 70 eV. Microanalyses were performed using a Hewlett-Packard 185 CHN Analyser.

Reaction of Chloroacetaldehyde with Ethyl Acetoacetate.—The method of Winberg *et al.*[10] was used for this reaction. The crude product (127.4 g), obtained from *ca.* 40% aqueous chloroacetaldehyde (78 cm^3) [prepared from chloroacetaldehyde diethyl acetal (104 g, 0.68 mol) by the procedure of Natterer [25]] and ethyl acetoacetate (90 g, 0.69 mol) was a 1 : 1 mixture of the furoate (12a) and ethyl acetoacetate (n.m.r. spectroscopy). After removal of the ethyl acetoacetate (by repeated washing of an ether solution of the product with 25% aqueous sodium hydrogensulphate), ethyl 2-methyl-3-furoate (12a) (69.5 g, 66% based upon chloroacetaldehyde diethyl acetal) was obtained as a colourless liquid; δ ($CDCl_3$) 1.35 (3 H, s, t, *J* 8 Hz, O·CH$_2$*Me*), 2.55 (3 H, s, CMe), 4.30 (2 H, q, *J* 8 Hz, O·C*H*$_2$Me), and 6.67 and 7.20 (each 1 H, d, *J* 2 Hz, OC*H*=C*H*C).

Reaction of the Ethyl Furoate (12a) *with Lithium Aluminium Hydride.*—The literature procedure [10] was adopted for this reaction. The crude product, obtained from the furoate (12a) (23.6 g, 0.15 mol) and lithium aluminium hydride (5.00 g, 0.13 mol), was purified by silica-gel chromatography [Et$_2$O–light petroleum (1 : 2) as eluant] to give 3-hydroxymethyl-2-methylfuran (12b) (8.92 g, 52%) as a colourless liquid; δ ($CDCl_3$) 2.23 (3 H, s, CMe), 3.72 (1 H, s, CH$_2$O*H*, disappears on addition of D$_2$O), 4.28 (2 H, s, C*H*$_2$OH), and 6.22 and 7.12 (each 1 H, d, *J* 2 Hz, O·CH=CH·C); *m/e* 112 (M^+) and 94 (M^+ − H$_2$O, base peak) (Found: M^+, 112.0534. Calc. for $C_6H_8O_2$: *M*, 112.0524).

Reaction of the Furan (12b) *with Bromine–Methanol.*—The conditions for this reaction were modelled upon those reported by Lee.[11] A stirred, cooled (Me$_2$CO–solid CO$_2$) solution of the furan (12b) (8.46 g, 75.5 mmol) in methanol–ether (4 : 1, 225 cm^3) was treated by adding in drops, during 2 h, bromine (12.1 g, 75.7 mmol) dissolved in methanol–ether (4 : 1; 80 cm^3). After a further 1.5 h, triethylamine (79.0 g, 187.8 mmol) was added to the mixture, which was then allowed to warm to room temperature. Ether was added to the mixture, which, after washing with brine, was dried (MgSO$_4$) and evaporated to give 2,5-dihydro-3-hydroxymethyl-2,5-dimethoxy-2-methylfuran (11) (10.5 g, 80%) as a yellow-green oil. The material, which was a 1 : 1 mixture of the diastereoisomers by n.m.r. spectroscopy, was sufficiently pure to be used in the subsequent reaction.

A sample, after purification by silica gel chromatography [Et$_2$O–light petroleum (1 : 2) as eluant], was obtained as a colourless, chromatographically homogeneous oil; $\nu_{max.}$ (film) 3 440br (OH) and 1 650 cm^{-1} (C=C); $\lambda_{max.}$ (EtOH) 217 nm (ε 400); δ ($CDCl_3$) 1.53 and 1.56 (3 H, each s, CMe), 3.04, 3.12, 3.37, and 3.48 (6 H, each s, 2 × OMe), 3.28 (1 H, s, CH$_2$O*H*), 4.10—4.20 (2 H, m, C·C*H*$_2$OH, disappears on addition of D$_2$O), 5.35—5.40 and 5.62—5.67 (1 H, each m, C*H*OMe), and 5.80—5.90 (1 H, m, HC=C); *m/e* 174 (M^+) and 31 (MeO^+, base peak) (Found: M^+, 174.0886. $C_8H_{14}O_4$ requires *M*, 174.0892).

Reaction of the Furan (11) *with Phosphate Buffer at pH* 6.3.—The conditions developed by Floyd [12] were adopted for this reaction. A solution of the furan (11) (10.2 g, 58.6 mmol) in dioxan (90 cm^3), water (60 cm^3), and phosphate buffer (pH 6.3, 150 cm^3) was treated with hydroquinone (0.1 g) and the mixture was heated under reflux for 1 h, after which time the starting material had disappeared (t.l.c.). Evaporation of the solvent left a residue which was dried by azeotropic distillation using ethanol. The residue was extracted several times with boiling ethyl acetate and the extracts were evaporated to leave a dark yellow oil which was purified by silica-gel chromatography (EtOAc as eluant) to give the racemate of 4-*hydroxy*-2-*hydroxymethylcyclopent*-2-*enone* (9a) (3.75 g, 50%), m.p. 57—59 °C (from EtOAc); $\nu_{max.}$ (KBr) 3.420br (OH), 1 700 (enone CO), and 1 645 cm^{-1} (C=C); $\lambda_{max.}$ (EtOH) 225 nm (ε 7 800); δ (CD_3COCD_3) 2.20 (1 H, d, *J* 16 and 3 Hz, CO·C*H*H·CH), 2.80 (1 H, dd, *J* 16 and 6 Hz, CO·CH*H*·CH), 2.90—3.20 (1 H, br m, OH, disappears on addition of D$_2$O), 4.15—4.30 (2 H, m, C*H*$_2$-OH), 4.20—4.60 (1 H, br m, OH, disappears on addition of D$_2$O), 4.75—5.00 (1 H, m, CH$_2$·C*H*·OH), and 7.30—7.40 (1 H, m, CH·C*H*=C); *m/e* 128 (M^+) and 110 (M^+ − H$_2$O, base peak) (Found: C, 56.5; H, 6.45. $C_6H_8O_3$ requires C, 56.2; H, 6.30%).

Thermolysis of Quinic Acid (17a).—A modification of the procedure of Wolinsky *et al.*[18] was adopted. D-(−)-Quinic acid (17a) (4.00 g) was heated until just molten and maintained in that state for 10 min. The product, which solidified on cooling to give a light brown, translucent glass, was purified by sublimation under reduced pressure (230 °C, 0.9—0.6 mmHg) to give the quinide (20a) (1.98 g, 55%) as a white solid, m.p. 175—182 °C and $[\alpha]_D$ −15° (1% in H$_2$O) [lit.,[18] 175—195 °C and −17° (H$_2$O)]; $\nu_{max.}$ (KBr) 3 400br (OH) and 1 785 cm^{-1} (γ-lactone CO); δ (D$_2$O) 1.70—2.50 (4 H, m, CH$_2$·C·CH$_2$), 3.70—4.30 (2 H, m, CH·OD·CH·OD), and 4.85—5.05 (1 H, m, CH·O·CO); *m/e* 175 (MH^+) and 112 ($C_6H_8O_2^+$, base peak) (Found: MH^+, 175.0608. Calc. for $C_7H_{11}O_5$: *M*, 175.0606).

Reaction of Quinic Acid (17a) *with Acetone.*—A modification of the literature method [20] was employed. A mixture of D-(−)-quinic acid (17a) (5.00 g), anhydrous sodium sulphate (25 g), concentrated sulphuric acid (0.15 cm^3), and acetone (250 cm^3) was heated under reflux for 1 h. After neutralisation with sodium hydrogencarbonate, the mixture was filtered and the filtrate was evaporated. The residue was partitioned between chloroform and water and the organic layer was dried (MgSO$_4$) and evaporated to give 3,4-*O*-isopropylidenequinide (22a) (4.01 g, 72%) as a white solid, m.p. 136—138 °C (from EtOH–light petroleum) and

$[\alpha]_D$ −28° (1.08% in EtOH) [lit.,[20] 140—141 °C and −36° (C_2Cl_4)]; $\nu_{max.}$ (KBr) 3 400 (OH) and 1 770 cm^{-1} (γ-lactone CO); δ ($CDCl_3$) 1.34 and 1.53 (each 3 H, s, CMe_2), 2.00—2.80 (4 H, m, $CH_2{\cdot}C{\cdot}CH_2$), 3.10 (1 H, br s, OH, disappears on addition of D_2O), and 4.10—4.80 (3 H, m, CH·CH·CH); *m/e* 199 (M^+ − Me, base peak) (Found: C, 56.0; H, 6.55. Calc. for $C_{10}H_{14}O_5$: C, 56.1; H, 6.54%).

Reaction of the Quinide (22a) *with Ethyl Chloroformate.*—Following the procedure of De Pooter *et al.*,[21] the isopropylidenequinide (22a) (3.70 g), was converted into 1-*O*-ethoxycarbonyl-3,4-*O*-isopropylidenequinide (22b) (4.87 g, 98%), m.p. 103—104 °C (from EtOH–H_2O) (lit.,[21] 106—107 °C); $[\alpha]_D$ −24° (1.5% in EtOH); $\nu_{max.}$ (KBr) 1 800 (γ-lactone CO) and 1 740 cm^{-1} (carbonate CO); δ ($CDCl_3$) 1.33 (3 H, t, *J* 7 Hz, CH_2*Me*), 1.33 and 1.48 (each 3 H, s, CMe_2), 2.20—3.20 (4 H, m, $CH_2{\cdot}C{\cdot}CH_2$), 4.18 (2 H, q, *J* 7 Hz, OCH_2Me), and 4.00—4.90 (3 H, m, CH·CH·CH); *m/e* 271 (M^+ − Me) and 43 (base peak).

Reaction of the Quinide (22b) *with Acetic Acid.*—A solution of the quinide (22b) (2.02 g) in acetic acid (10 cm^3) and water (10 cm^3) was heated at 60—70 °C for 18 h. Evaporation gave 1-*O*-ethoxycarbonylquinide (20b) (1.73 g, 100%) as a chromatographically homogeneous oil; $[\alpha]_D$ −17° (1.2% in EtOH); $\nu_{max.}$ (film) 3 400 (OH), 1 780 (γ-lactone CO), and 1 740 cm^{-1} (carbonate CO); δ ($CDCl_3$) 1.35 (3 H, t, *J* 7 Hz, *Me*CH_2), 2.00—3.20 (4 H, m, $CH_2{\cdot}C{\cdot}CH_2$), 3.80—4.60 (6 H, m, CH·OH·CH·OH and O·CH_2Me, simplified and integral reduced to 4 H on addition of D_2O), and 4.85—5.00 (1 H, m, CHO·CO); *m/e* 247 (MH^+) and 43 (base peak).

Reaction of Quinic Acid (17a) *with Methanolic Hydrogen Chloride.*—D-(−)-Quinic acid (17a) (20.0 g) was heated under reflux in methanol (250 cm^3) to which acetyl chloride (0.1 cm^3) had been added. Evaporation after 1 h gave methyl quinate (17b) (21.5 g, 100%) as a colourless oil which slowly crystallised, m.p. 124—127 °C (lit.,[26] 120 °C); $[\alpha]_D$ −43° (1.2% in H_2O); $\nu_{max.}$ (KBr) 3 400 (OH) and 1 720 cm^{-1} (ester CO); δ (D_2O) 1.80—2.30 (4 H, m, $CH_2{\cdot}C{\cdot}CH_2$), 3.40—4.30 (3 H, m, CH·OD·CH·OD·CH·OD), and 3.73 (3 H, s, CO_2Me); *m/e* 206 (M^+).

Reaction of Methyl Quinate (17b) *with Ammonia.*—A cooled (ice-bath) solution of methyl quinate (17b) (10.0 g) in methanol (250 cm^3) was saturated with ammonia. Evaporation after 48 h gave a foam which was dissolved in hot ethanol. Filtration and evaporation gave quinamide (17c) (6.86 g, 74%) as a white solid, m.p. 138—146 °C (lit.,[26] 132 °C); $[\alpha]_D$ −55° (1.06% in H_2O); $\nu_{max.}$ (KBr) 3 160—3 480 (OH and NH) and 1 667 cm^{-1} (amide CO); δ (D_2O) 1.86—2.20 (4 H, m, $CH_2{\cdot}C{\cdot}CCH_2$) and 3.35—4.35 (3 H, m, CH·OD·CH·OD·CH·OD); *m/e* 191 (M^+) and 147 (M^+ − CH_2ON, base peak).

Reaction of Quinamide (17c) *with Acetone.*—The method of Fischer and Dangschat [22] was employed. Quinamide (17c) (3.68 g) was shaken for 48 h with acetone (250 cm^3) through which hydrogen chloride had been vigorously bubbled for 30 s. Lead carbonate (10 g) and anhydrous magnesium sulphate (10 g) were added and the mixture was stirred for 2 h. Filtration through Celite and evaporation left a light yellow oil which was fractionated by silica-gel chromatography [EtOAc–light petroleum (9 : 1) as eluant].

The first-eluted compound, isolated as a white solid (0.578 g, 14%), was identical (t.l.c., n.m.r., i.r., and mass spectroscopy) with the quinide (22a).

The second-eluted material (1.96 g, 38%) was considered to be 1,1′-*ON*-isopropylidene-3,4-*O*-isopropylidenequinamide (27a), m.p. 126—128 °C (from EtOAc–light petroleum) and $[\alpha]_D$ −27° (1.25% in EtOH) [lit.,[22] 122 °C and −27° (EtOH)]; $\nu_{max.}$ (KBr) 3 540 and 3 320 (OH and NH) and 1 695 cm^{-1} (amide CO); δ (CD_3SOCD_3) 1.16—1.28 (3 H, and 9 H, each s, 2 × CMe_2), 1.40—2.00 (4 H, m, $CH_2{\cdot}C{\cdot}CH_2$), 3.50—4.50 (3 H, m, O·CH·CH·CH·O), 4.90 (1 H, d, *J* 5 Hz, CH·O*H*, disappears on addition of D_2O), and 8.87 (1 H, br s, CONH, disappears on addition of D_2O); *m/e* 271 (M^+) and 58 ($C_3H_6^+$, base peak).

Reaction of the Quinamide (27a) *with Benzoyl Chloride.*—A stirred, cooled (CCl_3–solid CO_2) solution of the quinamide (27a) (2.97 g, 11.0 mmol) in pyridine (20 cm^3) was treated with benzoyl chloride (1.63 g, 11.6 mmol), added in drops. The mixture was allowed to warm to room temperature after 1 h. After 48 h the mixture was poured into water and the solution was extracted with ethyl acetate. The extract was washed successively with dilute hydrochloric acid and water, and then dried ($MgSO_4$). Evaporation gave an oil which, on trituration with light petroleum, afforded 5-O-*benzoyl*-1,1′-ON-*isopropylidene*-3,4-O-*isopropylidene-quinamide* (27b) (3.52 g, 86%) as a white solid, m.p. 122—123 °C (from Et_2O–light petroleum); $[\alpha]_D$ −35° (1.7% in EtOH); $\nu_{max.}$ (KBr) 3 460br (NH) and 1 705br cm^{-1} (ester and amide CO); δ ($CDCl_3$) 1.37, 1.45, and 1.53 (3 H, 6 H, and 3 H, each s, 2 × CMe_2), 1.90—2.50 (4 H, m, $CH_2{\cdot}C{\cdot}CH_2$), 4.10—4.80 (2 H, m, O·CH·CH·O), 5.20—5.65 (1 H, m, C*H*·O·COPh), 7.20—7.60 and 7.90—8.20 (3 H and 2 H, each m, Ph), and 8.30 (1 H, br s, CO·NH, disappears on addition of D_2O); *m/e* 360 (M^+ − Me) and 43 ($CHNO^+$, base peak) (Found: C, 64.2; H, 6.75; N, 3.5. $C_{22}H_{25}NO_6$ requires C, 64.0; H, 6.67; N, 3.73%).

Reaction of the Quinamide (27b) *with Acetic Acid.*—A solution of the amide (27b) (3.52 g) in acetic acid (10 cm^3) and water (10 cm^3) was heated at 60—70 °C for 2 h. Evaporation left a residue which crystallised on addition of ether. Filtration gave 5-O-*benzoyl*-1,1′-ON-*isopropylidene-quinamide* (26) (2.56 g, 82%), m.p. 164—167 °C (from Et-OAc–light petroleum); $[\alpha]_D$ −19° (0.9% in EtOH); $\nu_{max.}$ (KBr) 3 480, 3 420, and 3 200 (OH and NH) and 1 700br cm^{-1} (ester and amide CO); δ (CD_3SOCD_3) 1.35 (6 H, s, Me_2C), 1.70—2.10 (4 H, m, $CH_2{\cdot}C{\cdot}CH_2$), 3.25—3.70 and 3.90—4.25 (1 H and 2 H, each m, HO·CH·CH·O, reduced to 2 H on addition of D_2O), 4.85 (1 H, d, *J* 6 Hz, CH·O*H*, disappears on addition of D_2O), 5.05—5.50 (1 H, m, C*H*·O·COPh), and 7.30—7.65 and 7.93—8.20 (3 H and 2 H, each m, Ph), and 8.95 (br, CO·NH, disappears on addition of D_2O); *m/e* 335 (M^+) and 105 ($C_7H_5O^+$, base peak) (Found: C, 60.9; H, 6.4; N, 4.05. $C_{17}H_{21}NO_6$ requires C, 60.9; H, 6.27; N, 4.18%).

Reaction of the Quinamide (26) *with Sodium Periodate followed by Pyrrolidinium Acetate.*—A stirred solution of the diol (26) (3.10 g, 9.25 mmol) in THF (1.50 cm^3) was treated with sodium periodate (1.99 g, 9.30 mmol) in water (50 cm^3). Evaporation after 2.5 h left a residue which, after drying by azeotropic distillation using benzene, was mixed with benzene (100 cm^3) and anhydrous sodium sulphate (10 g). A solution of benzene (10 cm^3) containing pyrrolidine (4 drops) and acetic acid (2 drops) was added to the mixture which was then heated at 50—60 °C for 1.5 h. After filtration and washing the residue with ethyl acetate, the solution was shaken with dilute hydrochloric acid, water, and brine. Evaporation of the dried ($MgSO_4$) organic layer gave an orange-coloured oil which was purified by silica-gel chromatography (Et_2O as eluant) to give (5R,8R)-8-*benzoyloxy*-2,2-*dimethyl*-4-*oxo*-1-*oxa*-3-*azaspiro*[4.4]*non*-6-*ene*-6-*carbaldehyde* (32) (1.94 g, 67%), m.p. 212 °C (from

CH_2Cl_2–light petroleum); $[\alpha]_D$ +87° (1% in EtOH); $\nu_{max.}$ (KBr) 3 320 (NH), 1 720 (ester CO), and 1 685 cm^{-1} (amide and αβ-unsaturated aldehyde CO); $\lambda_{max.}$ (EtOH) 230 (ε 20 200), 273sh (1 100), and 281sh nm (920); δ ($CDCl_3$) 1.52 and 1.58 (each 3 H, s, CMe_2), 2.38—3.00 (2 H, 2 AB q, *J* 14.5, 6, and 7 Hz, C·CH_2·CH·O), 6.32 (1 H, d of dd, *J* 2, 6, and 7 Hz, C*H*·O·COPh), 7.16 (1 H, d, *J* 2 Hz, CH·C*H*=C), 7.40—7.60 and 7.85—8.20 (each 3 H, m, Ph and CONH, addition of D_2O reduced intensity to 2 H), and 9.85 (1 H, s, CHO); δ_C ($CDCl_3$) 28.0 and 30.3 (each q, *Me*$_2$C), 43.9 (t, CH_2), 76.8 (d, *C*H·O·COPh), 87.7 and 91.3 (each s, CO·*C*·O and *C*Me_2), 128.5, 129.4, and 133.5 (each d, *o*-, *m*-, and *p*-C of Ph), 129.8 (quaternary C of Ph), 145.8 (d, *C*=CH), 152.5 (d, *C*H=C) 166.3 (s, Ph*C*O·O), 172.2 (s, CO·NH), and 187.3 (d, CHO) (the multiplicities were determined by off-resonance decoupling; the signal at 129.8 was obscured and that at 145.8 appeared as a closely spaced d in the off-resonance decoupled spectrum); *m/e* 315 (M^+) and 105 ($C_7H_5O^+$, base peak) (Found: C, 64.6; H, 5.15; N, 4.2. $C_{17}H_{17}NO_5$ requires C, 64.8; H, 5.40; N, 4.44%).

Reaction of the Carbaldehyde (32) *with Lithium Borohydride*.—A solution of the aldehyde (32) (0.449 g, 1.43 mmol) in THF (20 cm^3) was treated with lithium borohydride (0.500 g, 23 mmol) and the mixture was heated under reflux. After 18 h, methanol followed by Amberlite IR 120 (H^+) ion-exchange resin were added to the ice-cooled solution. Filtration and evaporation gave an oil which was repeatedly dissolved in methanol and re-evaporated. Purification of the product (0.380 g) by silica-gel chromatography (EtOAc as eluant) gave (5R,8R)-8-*hydroxy*-6-*hydroxymethyl*-2,2-*dimethyl*-1-*oxa*-3-*azaspiro*-[4.4]*non*-6-*en*-4-*one* (34a) (0.093 g, 31%), m.p. 157—158 °C (from EtOAc–light petroleum); $[\alpha]_D$ −80° (1.1% in EtOH); $\nu_{max.}$ (KBr) 3 400 and 3 280 (OH and NH) and 1 705 and 1 660 cm^{-1} (amide CO); δ (CD_3COCD_3) 1.50 (6 H, s, CMe_2), 1.90—2.30 (m, C·CH_2·CH, partly obscured by solvent signals), 3.60 (1 H, d, *J* 11 Hz, CH·O*H*, disappeared on addition of D_2O), 3.90 (1 H, br t, *J* 5 Hz, CH_2·O*H*, disappears on addition of D_2O), 4.10—4.25 (2 H, m, CH_2·OH, sharpened on addition of D_2O), 4.35—4.80 (1 H, m, C*H*·OH, sharpened on addition of D_2O), 6.00—6.10 (1 H, m, CH·C*H*=C), and 8.20 (1 H, br s, CO·NH, disappears on addition of D_2O); *m/e* 214 (MH^+) and 129 (base peak) (Found: C, 56.4; H, 7.15; N, 6.7. $C_{10}H_{15}NO_4$ requires C, 56.3; H, 7.04; N, 6.57%).

Reaction of the Carbaldehyde (32) *with Sodium Borohydride*.—A stirred, cooled (CCl_4–solid CO_2) solution of the aldehyde (32) (0.538 g, 1.71 mmol) in THF (10 cm^3) was treated with sodium borohydride (0.100 g, 2.64 mmol). The mixture was allowed to warm to room temperature and, after 30 min, cautiously acidified with 1M-hydrochloric acid and extracted with ethyl acetate. Evaporation of the dried ($MgSO_4$) organic layer gave a colourless oil (0.537 g, 99%) which was (5R,8R)-8-*benzoyloxy*-6-*hydroxymethyl*-2,2-*dimethyl*-1-*oxa*-3-*azaspiro*[4.4]*non*-6-*en*-4-*one* (34b), m.p. 215—217 °C (from CH_2Cl_2–light petroleum); $[\alpha]_D$ +62° (1.0% in EtOH); $\nu_{max.}$ (KBr) 3 440 and 3 290 (OH and NH), 1 705 (ester CO), and 1 685 cm^{-1} (amide CO); δ ($CDCl_3$) 1.45 (6 H, s, CMe_2), 2.20—2.90 (2 H, m, CH_2·CH), 2.90—3.10 (1 H, br s, CH_2·O*H*, disappears on addition of D_2O), 4.20 (2 H, br s, CH_2·OH), 5.80—6.15 (1 H, m, C*H*·OCOPh), 6.20—6.30 (1 H, m, CH·C*H*=C), 7.20—7.50 and 7.90—8.10 (3 H and 2 H, each m, Ph), and 8.35 (1 H, br s, CO·NH, disappears on addition of D_2O); *m/e* 317 (M^+) and 105 (base peak) (Found: C, 63.9; H, 5.85; N, 4.35%; M^+, 317.1275. $C_{17}H_{17}NO_5$ requires C, 64.3; H, 5.99; N, 4.42%; *M*, 317.1263).

Reaction of the Benzoate (34b) *with Sodium Methoxide*.—A solution of the benzoate (34b) (0.260 g, 0.82 mmol) in methanol (10 cm^3) was treated with 25% sodium methoxide solution (0.7 cm^3). After 12 h the mixture was neutralised with Amberlite IR 120 (H^+) ion-exchange resin. Evaporation of the solvent gave a light yellow oil which was subjected to silica-gel chromatography. The first-eluted material [EtOAc–light petroleum (1 : 2) as eluant] was methyl benzoate (n.m.r. spectroscopy). The second-eluted material (0.139 g, 80%) [EtOAc–EtOH (9 : 1) as eluant] was identical (t.l.c., n.m.r., and i.r. spectroscopy) with the diol (34a).

Reaction of the Oxazolidinone (34a) *with Hydrazine*.—A solution of the oxazolidinone (34a) (0.180 g, 0.85 mmol) in hydrazine hydrate (1.5 cm^3) was heated under reflux for 4 h. Evaporation left a light yellow oil which was purified by silica-gel chromatography [EtOAc–EtOH (2 : 1) as eluant] to give (1*R*,4*R*)-1,4-dihydroxy-2-hydroxymethylcyclopenten-2-ene-1-carbohydrazide (35a) (0.127 g, 80%) as a colourless oil; $[\alpha]_D$ −42° (1.6% in EtOH); $\nu_{max.}$ (film) 3 300br (OH and NH) and 1 675 cm^{-1} (acid hydrazide CO); δ (D_2O) 2.20—2.40 (2 H, m, CCH_2·CH·O), 4.10—4.20 (2 H, m, CH_2·OH), 4.80—5.10 (1 H, m, C*H*·OH), and 6.00—6.10 (1 H, m, CH·C*H*=C); *m/e* 170 ($M^+ - H_2O$) and 111 ($C_6H_7O_2^+$, base peak).

Reaction of the Carbohydrazide (35a) *with Nitrous Acid and Thermolysis of the Product*.—An ice-cold solution of sodium nitrite (0.350 g, 5.1 mmol) in water (5 cm^3) was treated with Amberlite IR 120 (H^+) ion-exchange resin. The aqueous nitrous acid was decanted into a cold flask and treated with an ice-cold solution of the hydrazide (35a) (0.220 g, 1.17 mmol) in water (20 cm^3), added in drops. After 30 min at *ca.* 0 °C the solvent was evaporated to give the azide (35b) as an oil; $\nu_{max.}$ (film) 3 260 (OH), 2 120 (N_3), and 1 700 cm^{-1} (acid azide CO). A solution of the azide (35b) in water was heated at 50—60 °C for 30 min. Evaporation and purification of the product by silica-gel chromatography (EtOAc as eluant) gave (4*R*)-4-hydroxy-2-hydroxymethylcyclopent-2-en-1-one (9a) (0.092 g, 42%) as a colourless oil which was identical (n.m.r. and mass spectroscopy) with the product obtained from the dihydrofuran (11); $[\alpha]_D$ +50° (0.9% in EtOH); $\lambda_{max.}$ (EtOH) 222 nm (ε 5 300) (Found: M^+, 128.0484. $C_6H_8O_3$ requires *M*, 128.0473).

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