SOME APPLICATIONS OF THE KNOEVENAGEL REACTION IN THE CARBOHYDRATE FIELD

F. J. LOPEZ APARICIO,

Department of Organic Chemistry, University of Granada (Spain) F. J. LOPEZ HERRERA, AND J. SANCHEZ BALLESTEROS Department of Organic Chemistry, University of Malaga (Spain) (Received September 29th, 1977; accepted for publication, October 10th, 1977)

ABSTRACT

The reaction of 2,3-O-isopropylidene-D-glyceraldehyde (1) with active methylene compounds in the absence of a catalyst involves facile and reversible addition to the formyl group. The adducts are readily transformed into furan derivatives by acid hydrolysis. When the reaction is catalysed with piperidine, unsaturated products are also formed, including α,β - and β,γ -unsaturated dicarbonyl compounds, which are transformed into furan derivatives *via* hydrolysis of the acetal group. A new type of unsaturated compound having a spiro-ketal structure is also produced as a result of intramolecular cyclisation.

INTRODUCTION

Application of the Knoevenagel reaction to aldehydo sugars was first described by Papadakis¹ and by Garcia Gonzalez and Lopez Aparicio². The reaction provides a new route for the synthesis of modified sugars³ and appears to be related to the synthesis of furan compounds from monosaccharides⁴. We now report on other aspects of this reaction.

Only for the reactions of 2,3-O-isopropylidene-D-glyceraldehyde (1) with ethyl acetoacetate² (2a) and dibenzoylmethane³ have the intermediate adducts been



detected or isolated. In all other cases, either for 1 or for other aldehydo sugars, only α,β -unsaturated products of the type 6 have been described³. Some decarboxylation products were obtained when R¹ or R² was OH. The identification of 3a presented a problem, because of the coincidence of its elemental composition with those of the reagents 1 and 2a; the boiling point was also unexpectedly low.

The reaction of 1 with methyl acetoacetate (2b) was therefore studied. With piperidine catalysis, 3b was formed; 3b could be isolated and characterised, and its transformation into the furan derivative 5b monitored by n.m.r. spectroscopy.

Under conditions of piperidine catalysis, unsaturated products also are always formed. In the reactions of 1 with pentane-2,4-dione (2c), ethyl benzoylacetate (2d), and benzoylacetone (2e), the respective adducts 3c, 3d, and 3e could not be isolated free from contamination by the initial reagents. However, their formation was demonstrated on the basis of spectroscopic data. The failure to remove the contaminants suggested that the reactions were reversible during distillation of the products and that reaction can proceed without a catalyst. The catalyst or high temperature also promotes the dehydration of 3, to yield such unsaturated compounds as 6 or its isomers. It was demonstrated that the reaction without a catalyst was exothermic and practically quantitative. The absence of the reagents in the mixture after a short reaction time at room temperature was demonstrated by i.r. and n.m.r. spectroscopy.

The transformation of 3a into 5a in the presence of pentane-2,4-dione (2c) indicated² that the formation of 3a was an irreversible process. But when a mixture of 3b and 2c was heated and then hydrolysed with acid, a mixture of 5b and 5c was formed. Thus, the earlier conclusions would be explained if the relative velocity of the process $3 \rightarrow 5$ was much greater than that of the process $3 \rightarrow 2$. A mixture of 5b and 5c was also obtained by condensing 3b and 2c in the vapour phase, *in vacuo*, and then hydrolysing the product.

Although the Knoevenagel reaction of 1 with active methylene compounds of type 2 gave products having elemental analyses conforming to formula 6, it was possible to identify or isolate up to four isomers (6-9) in various proportions. The complexity of these mixtures may be greater, since E and Z isomers are possible for some of the unsaturated products. In general, only the more stable isomers could be isolated pure, and the spiro-ketals 9 could be obtained by the action of heat or acid catalysis in an aprotic solvent on the isomers 6-8.

In the reaction of 2c, isomers 6c and 7c were formed, as shown by t.l.c. and spectroscopy. The isomer 8c was not formed, probably because its stability is much lower than that of the corresponding enol 7c. The isomerization $6c \rightarrow 7c$ was accomplished by the action of a partially neutralised, acid resin. Since the spectrum of 7c is known, that of 6c could be deduced from a ~1:1 mixture of the compounds. The signals of vinyl protons [δ 6.6 (d, ³J 6 Hz) for the α,β -unsaturated product 6c, and 5.3 (t, ⁴J 1.2 Hz) for the β,γ -unsaturated isomer 7c (enol)] were important in the interpretation of the n.m.r. spectra of mixtures.

For the reaction of methyl malonate (2f), the situation in relation to the enol stability is the opposite of that noted for the enol 7c. The β , γ -unsaturated diester 8f



is the stable form and can be isolated. Once the spectrum of 8f was known [δ 5.0 (dt, ³J 10, ⁴J 1 Hz, =CH)], it was possible to deduce that, under mild conditions, the α , β -unsaturated isomer was among the reaction products [δ 6.8 (d, =CH)] and must be formed first and then transformed into 7 and 8.

The reactions of 1 with 2b and 2a appear to be intermediate between the abovementioned cases, on the basis of the relative stability of isomers 7 and 8. The reaction products were mixtures of four isomers, as shown by n.m.r. spectroscopy. The interpretation of these spectra could be accomplished (a) by subtraction of the signals for 9, (b) by using the data for the c and f series of isomers, and (c) by correlating the intensities of sets of signals having the same proportions of components in a mixture. The most-prominent signals associated with this analysis were for Ac (*E*-6, δ 2.32–2.34; Z-6, 2.16–2.28; 8, 2.13–2.19; 7, 1.97–2.08) and -CH [6, δ 6.82–6.74 (*trans* to -COOR) and 6.70–6.60 (*trans* to Ac); 7 and 8, 5.3–5.0].

The piperidine-catalysed reactions of 1 and ethyl benzoylacetate (2d) or benzoylacetone (2e) were exothermic, but the products, after distillation, contained only 9d and 9e-g, respectively. Thus, both Ac and Bz groups can participate in ring formation.



The formation of 9 involves a process subsequent to the Knoevenagel reaction. Although it is better produced by acid catalysis, it can also result by distillation of the other isomers. We have not found any precedent for this reaction, and consequently the structure and properties of this new type of spiro-ketal 9 have been studied. From the type of catalysis and structural change, the formation of 9 can be considered to involve an intramolecular addition to a vinyl ether. The participation of the electron-releasing oxygen atom may be the reason why this type of compound is not a product of a normal Knoevenagel reaction.

The structure of 9 is indicated by spectroscopic data; e.g., for 9b, λ_{max} 248 nm ($\varepsilon 1.07 \times 10^4$). The two diastereotopic hydrogens in the dioxolane ring appear as AB systems in the n.m.r. spectra (in CDCl₃ or CCl₄), but those in the dihydrofuran residue are accidentally equivalent and long-range coupled to Me-2 for all spiro-ketals with $R^1 = Me$, or as a simple signal for those with $R^1 = Ph$ if the spectra were in CDCl₃ or CCl₄. The diastereotopic character could be clearly observed for benzene solutions. In the i.r. spectra, only a carbonyl stretching band was observed. The structures 9 were also indicated by a negative enol test, the formation of one mono-semicarbazone from 9c, and the basic hydrolysis of the ester group in 9b to yield an acid which did not decarboxylate under conditions in which β -keto acids react. The group R^2 in 9 may be widely varied without altering the remaining structure, e.g., $9b \rightarrow 9h \rightarrow 9i \rightarrow 9j$, $9h \rightarrow 9c$, and $9d \rightarrow 9k \rightarrow 9e$.

The formation of two isomers **9e** and **9g** starting with benzoylacetone is strong, additional evidence for the assigned structures, as is the transformation:

HO⁻ LiMe 9a \rightarrow 9h \rightarrow 9c.

When the spiro compounds of type 9 were treated with acid in an aprotic solvent



under more drastic conditions, acetone was removed and a new type of product was formed for which spectroscopic data indicated the structure 17. The u.v. spectra were quite similar to those of compounds of type 9, reflecting the presence of the same chromophore system. The ¹H-n.m.r. spectra were also similar, except for the signals of the CMe₂ group. The presence of the fragment m/e 170 in the mass spectrum of 17b suggests that the product has a centrosymmetrical, *trans* configuration, in accordance with the fragmentation process $18 \rightarrow 19 + 20$ which involves hydrogen transfer. An X-ray crystal-structure determination is in progress.

Acid hydrolysis of 9a, 9b, and 9d in aqueous media cleaved the dioxolane and dihydrofuran rings, yielding the diketonic esters 11a, 11b, and 11d, respectively. Periodate oxidation of 9b afforded 12 which, on hydrolysis and decarboxylation, gave levulinic acid. Compounds 11a and 11b were hydrolysed in a basic medium, and the resulting β -keto acid was then decarboxylated to the hydroxydiketone 14a (or 14b). Similarly, 11d was transformed into 14d.

Although the synthesis of furan derivatives starting with unsaturated products obtained from pentane-2,4-dione was unsuccessful², a mixture of 6c and 7c can be transformed into the corresponding furan derivative 5c by treatment with acetic acid-water (1:1), or into the methylated derivative 15 when the hydrolysis was performed with an acid resin and methanol.

EXPERIMENTAL

General methods. — Melting points are uncorrected. I.r. spectra (KBr discs) were obtained with a Beckman Aculab IV spectrometer. ¹H-N.m.r. spectra were recorded for solutions in CCl₄ (internal Me₄Si) with Perkin–Elmer–Hitachi R-20B or Perkin–Elmer R-24B spectrometer. Chemical shifts (first order) are given on the δ scale, and first-order couplings in Hz.

Concentration of solutions was performed under diminished pressure at $<40^{\circ}$, using a rotary evaporator.

Addition of active methylene compounds 2 to 2,3-O-isopropylidene-D-glyceraldehyde (1). — (a) Without a catalyst. A mixture of 1 and 2 in equimolar proportions was stored for 12 h at room temperature. Evolution of heat was always observed. Each reaction was monitored by n.m.r. spectroscopy until the initial reagents could no longer be detected. The following products were obtained.

Adduct 3b [from methyl acetoacetate (2b)]; v_{max}^{film} 3480, 2980, 2940, 2890, 1735, 1715, 1630–1640, 1440, 1370, 1250, 1210, 1150, and 1015 cm⁻¹. ¹H-N.m.r. data: δ 3.30–4.40 (m, 9 H), 2.20 (s, 3 H, Ac), 1.30 and 1.24 (2 s, 6 H, CMe₂).

Adduct 3a [from ethyl acetoacetate (2a)], b.p. 50°/1 Torr; v_{max}^{film} 3480, 2980, 2930, 2900, 1735, 1715, 1635–1640, 1370, 1250, 1210, 1150, and 1070 cm⁻¹. ¹H-N.m.r. data: δ 3.5–4.2 (m, 9 H), 2.2 (s, 3 H, Ac), 1.30 and 1.25 (2 s, 6 H, CMe₂), and 1.25 (t, 3 H, ³J 6 Hz, OCH₂CH₃).

A second fraction, b.p. $98-104^{\circ}/0.5$ Torr, was obtained; this appeared to be a mixture of unsaturated isomers similar to that described below.

Adduct 3c [from pentane-2,4-dione (2c)], $[\alpha]_D^{20} + 47^\circ$ (c 2.59, benzene); ν_{max}^{film} 3450, 2980, 2920, 2860, 1715, 1615, 1415, 1370, 1250, 1210, 1150, and 1065 cm⁻¹. ¹H-N.m.r. data: δ 3.94 (b, 6 H, unresolved), 2.20 (s, 3 H, Ac), 2.00 (s, 3 H, Ac, enol), 1.33 and 1.27 (2 s, 6 H, CMe₂). A small excess of the initial reagents was observed even after a long time of reaction.

Adduct 3d [from ethyl benzoylacetate (2d)]; v_{max}^{film} 3450, 3050, 2970, 2930, 2890, 1730, 1680, 1615, 1590, 1575, 1515, 1450, 1370, 1260, 1210, 1150, 1060, and 750 cm⁻¹. ¹H-N.m.r. data: δ 7.29 (m, 5 H, Ph), 3.80–4.70 (m, 8 H), and 1.00–1.30 (m, 9 H, 3 Me).

Adduct 3e [from benzoylacetone (2e)]; v_{max}^{film} 3440, 3050, 2980, 2920, 2870, 1710, 1665, 1640, 1585, 1565, 1500, 1435, 1410, 1360, 1350, 1190, 1140, 1050, 1010, 830, and 750 cm⁻¹. ¹H-N.m.r. data: δ 7.20–8.00 (m, 5 H, Ph), 3.92 (b, 6 H), 2.10 (s, 3 H, Ac), 1.40 and 1.20 (2 s, CMe₂).

5-Hydroxymethyl-3-methoxycarbonyl-2-methylfuran (**5b**). — (a) A solution of **3b** (9.5 g) in ethanol (150 ml), acetic acid (150 ml), and water (100 ml) was heated at 80° for 24 h. Ethyl acetate (100 ml) was added, and the organic layer was washed successively with water (2 × 100 ml) and 5% aqueous sodium hydroxide (100 ml), dried (Na₂SO₄), and concentrated. Distillation of the residue yielded **5b** (5.1 g, 77%), b.p. 94–95°/0.1 Torr; λ_{max}^{EtOH} 248 (ϵ 4.37 × 10³) and 215 nm (ϵ 5.83 × 10⁴); ν_{max}^{film} 3420, 2970, 2920, 2900, 2840, 1680, 1670, 1585, 1550, 1430, 1420, 1375, 1345, 1275, 1205, 1115, 1070, 1000, 950, 900, 800, 750, and 660 cm⁻¹. ¹H-N.m.r. data: δ 6.32 (s, 1 H, H-4), 4.38 (s, 2 H, CH₂OH), 3.7 (s, 3 H, OMe), and 2.5 (s, 3 H, Ac). Mass spectrum: m/e: 170 (M⁺), 155 (M – Me), 153 (M – OH), 139 (M – CH₂OH), 127 (M – Ac), 111 (M – CO₂Me) or (M – CO – CH₂OH), 59 (CO – CH₂OH), and 43 (Ac).

Anal. Calc. for C₈H₁₀O₄: C, 56.52; H, 6.54. Found: C, 56.43; H, 6.32.

A solution of 3b in $CDCl_3$ was periodically shaken with a dilute solution of CF_3CO_2D in D_2O . The n.m.r. signals of the reagents gradually disappeared, simultaneously with the appearance of those for 5b.

(b) Reversibility of the addition reaction. A mixture of 3b (1 g) and 2c (0.41 g) was kept at room temperature for 30 min. Then, ethanol (1.5 ml), acetic acid (1.5 ml), water (1 ml), and conc. hydrochloric acid (3 drops) were added, and the mixture was heated at 80° for 1 h. Ethyl acetate (10 ml) was added, and the organic layer was washed successively with water (2 × 10 ml) and 5% aqueous sodium hydroxide (2 × 10 ml), dried (Na₂SO₄), and concentrated. The residue contained only 5b, as shown by n.m.r. spectroscopy, and by t.l.c. on silica gel (Merck 60 F₂₅₄; light petroleum–ethyl acetate, 9:1; R_F 0.45).

A similar mixture of 3b and 2c was heated at 100° for 30 min and then treated as described above. T.I.c. of the product revealed 5b (R_F 0.45) and 3-acetyl-5-hydroxymethyl-2-methylfuran (5c, R_F 0.67). ¹H-N.m.r. data δ 6.51 (s, 1 H, =CH), 4.55 (s, 2 H, -CH₂O-), 2.57 (s, 3 H, Me), and 2.39 (s, 3 H, Me).

When the vapours of 3b and 2c were condensed together, subsequent acid hydrolysis, as described above, yielded a mixture of 5b and 5c, as shown by t.l.c. and ¹H-n.m.r. spectroscopy.

Piperidine-catalysed reaction of 1 with active methylene compounds 2. — When 1 (25 g), 2b (21.5 g), and piperidine (6 drops) were mixed, the temperature rose to 50°. The mixture was kept in the dark for 12 h, and then distilled to yield 3b (6.2 g), b.p. $36-40^{\circ}/0.2$ Torr, and a second fraction (22.26 g, 39%), b.p. $92^{\circ}/0.2$ Torr, that appeared to be a mixture of the following isomers.

(a) Enol 7b: ¹H-n.m.r. data: δ 12.63 (s, 1 H, OH), 5.1–4.6 (m, 1 H, vinyl ether CH=), 4.23 (d, J 2 Hz, 2 H, dioxolane CH₂), 3.69 (s, 3 H, OMe), 1.97 (s, 3 H, Ac), 1.44 and 1.40 (2 s, 6 H, CMe₂).

(b) α,β -Unsaturated ketoester **6b**: ¹H-n.m.r. data: δ 6.82 (d, J 12 Hz, 1 H, =CH, *E* isomer), 6.70 (d, J 12 Hz, 1 H, =CH, Z isomer), 2.34 (s, 3 H, Ac, *E* isomer), 2.28 (s, 3 H, Ac, *Z* isomer), 3.77 (s, 3 H, OMe, *E*,*Z* isomers), 1.41 and 1.30 (2 s, 6 H, CMe₂).

(c) β , γ -Unsaturated ketoester 8b: ¹H-n.m.r. data: δ 5.1–4.6 (m, 1 H, vinyl ether = CH), 4.47 (d, 2 H, J 2 Hz, dioxolane CH₂), 3.67 (s, 3 H, OMe), 2.13 (s, 3 H, Ac), 1.44 and 1.40 (2 s, 6 H, CMe₂).

(d) Spiro-isomer 9b: ¹H-n.m.r. data given below.

Anal. of the mixture (a)–(d). Calc. for $C_{11}H_{16}O_5$: C, 57.90; H, 7.06. Found: C, 57.67; H, 7.28. Positive enol reaction with ferric chloride.

In toluene solution with piperidine-catalysis, the yield of unsaturated isomers was 50-75%, with various proportions of the isomers.

DL-8-Methoxycarbonyl-2,2,7-trimethyl-1,3,6-trioxaspiro[4.4]non-7-ene (9b). — A solution of the foregoing mixture of isomers (24 g) in CCl₄ (81 ml) and acetic acid (9 ml) was boiled under reflux for 1 h. Distillation yielded 9b (23.5 g, 98%), b.p. 94-96°/0.2 Torr, m.p. 43-44° (negative test for enol); λ_{max}^{EIOH} 248 nm (ε 1.07 × 10⁴); ν_{max}^{film} 2990, 2950, 2870, 1705, 1655, 1440, 1385, 1375, 1345, 1290, 1220, 1140, 1110, 1090, 1060, 970, 900, 850, 800, 750, and 670 cm⁻¹. ¹H-N.m.r. data: δ 4.10 and 3.78 (2 d, 2 H, J 8.4 Hz, dioxolane CH₂), 3.59 (s, 3 H, OMe), 2.91 (q, 2 H, J 1.6 Hz, dihydrofuran CH₂), 2.16 (t, 3 H, J 1.6 Hz, Me), 1.43 and 1.32 (2 s, 6 H, CMe₂). Mass spectrum: m/e 228 (M⁺), 213 (M – Me), 197 (M – OMe), and 170 (M – COMe₂). The fragments of furan 5b were also formed.

Anal. Calc. for $C_{11}H_{16}O_5$: C, 57.90; H, 7.06. Oxid. equiv. $(IO_4, after acid hydrolysis)$, 228. Found: C, 58.24; H, 6.95. Oxid. equiv., 208.

DL-8-Carboxy-2,2,7-trimethyl-1,3,6-trioxaspiro[4.4]non-7-ene (9h). — A solution of potassium hydroxide (1.68 g) in water (15 ml) was added to a solution of 9b (4.85 g) in ethanol (15 ml). After stirring for 30 min at room temperature, the mixture was stored for 48 h and then extracted with ether (3 × 100 ml). The aqueous layer was acidified (Congo Red) with 8% hydrochloric acid. The solid was collected, washed with cold water, and recrystallised from water, to give 9h (2.8 g, 61.5%), m.p. 116-118°; λ_{max}^{EtOH} 224 nm (ε 1.47 × 10⁴); v_{max}^{KBr} 3400–2560 (broad), 2980, 2900, 1670, 1430, 1370, 1335, 1305, 1270, 1225, 1150, 1105, 1085, 1060, 970, 920, 890, 880, and 840 cm⁻¹. ¹H-N.m.r. data (CDCl₃): δ 10.5–9.0 (bs, 1 H, CO₂H), 4.27 and 3.95 (2 d, 2 H, J 10 Hz, dioxolane CH₂), 3.02 (q, 2 H, J 2 Hz, dihydrofuran CH₂), 2.23 (t, 3 H, J 2 Hz, Me), 1.52 and 1.40 (2 d, 6 H, CMe₂).

Anal. Calc. for $C_{10}H_{14}O_5$: C, 56.07; H, 6.54. Found: C, 56.22; H, 6.71. DL-8-Acetyl-2,2,7-trimethyl-1,3,6-trioxaspiro[4.4]non-7-ene (9c). — To a solu-

tion of **9h** (2.6 g) in dry dimethoyethane (10 ml) was added dropwise, with stirring, a solution of methyl-lithium (0.6 g) in ether (7 ml) at <5°. Stirring was maintained for 3 h at room temperature, aqueous 30% ammonium chloride (15 ml) was added, and the suspension was extracted with ether (3 × 60 ml). The extract was dried (Na₂SO₄) and concentrated, and the residue was distilled to yield **9c** (0.75 g), b.p. 73-75°/0.2 Torr (negative haloform test); λ_{max}^{EtOH} 271 nm (ε 1.04 × 10⁵); ν_{max}^{film} 2980, 2925, 2860, 1670, 1625–1595, 1450, 1433, 1418, 1380, 1365, 1270, 1230, 1218, 1145, 1080, 1060, 1040, 965, 890, 840, 795, and 750 cm⁻¹. ¹H-N.m.r. data: δ 4.18 and 3.88 (2 d, 2 H, J 9 Hz, dioxolane CH₂), 3.0 (q, 2 H, J 1.8 Hz, dihydrofuran CH₂), 2.25 (t, 3 H, J 1.8 Hz, Me), 2.1 (s, 3 H, Ac), 1.5 and 1.4 (2 s, 6 H, CMe₂). Mass spectrum: m/e 212 (M⁺), 197 (M – Me), 154 (M – COMe₂), 139 (154 – Me), 137 (154 – OH), 111 (154 – Ac), 96 (154 – CO – CH₂O), and 43 (Ac).

Anal. Calc. for C₁₁H₁₆O₄: C, 62.66; H, 7.54. Found: C, 62.42; H, 7.75.

The semicarbazone of **9c** (78%) had m.p. 254–256° (from ethanol-water, 1:1). *Anal.* Calc. for C₁₂H₁₉N₃O₄: C, 53.53; H, 7.06; N, 5.61. Found: C, 53.60; H, 6.98; N, 5.60.

DL-8-Chloroformyl-2,2,7-trimethyl-1,3,6-trioxaspiro[4.4]non-7-ene (9i). — A mixture of 9h (3.56 g), carbon tetrachloride (21 ml), and triphenylphosphine (4.2 g) was boiled under reflux for 3 h, cooled to 0°, filtered, and concentrated to dryness. The residue was extracted with light petroleum (50 and 3 × 25 ml). The combined extracts were concentrated, and the residue was distilled to yield 9i (1.6 g, 43%), b.p. 87–90°/0.1 Torr; v_{max}^{film} 2980, 2920, 1755, 1700, 1630, 1430, 1420, 1405, 1360, 1340, 1260, 1200, 1115, 1040, 950, 880, 775, and 740 cm⁻¹. ¹H-N.m.r. data (CDCl₃): δ 4.29 and 3.98 (2 d, 2 H, J 9.6 Hz, dioxolane CH₂), 3.25 (q, 2 H, J 1.5 Hz, dihydrofuran CH₂), 2.23 (t, 3 H, J 1.5 Hz, Me), 1.51 and 1.41 (2 s, 6 H, CMe₂).

DL-8-Carbamoyl-2,2,7-trimethyl-1,3,6-trioxaspiro[4.4]non-7-ene (9j). — A solution of crude 9i (from 6.8 g of 9h) in light petroleum was stirred with 3.5 g of a suspension of sodium amide in toluene (1:1) for 2 h under anhydrous conditions and then boiled under reflux for 1 h. To the cooled (0°) mixture was added dropwise, with stirring, a solution of ammonium chloride (1.68 g) in water (6 ml) and then water (14 ml). The solid was collected, washed with cold water, and recrystallised from ethanol-water, to yield 9j (3.44 g, 51%), m.p. 160–162°; λ_{max}^{EOH} 246 nm (ϵ 1.1 × 10⁴); ν_{film}^{KBr} 3415, 3170, 2982, 2940, 1650, 1590, 1445, 1370, 1320, 1280, 1255, 1212, 1160, 1115, 1085, 1060, 1025, 960, 895, 840, and 760 cm⁻¹. ¹H-N.m.r. data (CDCl₃): δ 5.37 (b, 2 H, exchangeable with D₂O, NH₂), 4.31 and 3.97 (2 d, 2 H, J 8.4 Hz, dioxolane CH₂), 3.00 (q, 2 H, J 1.8 Hz, dihydrofuran CH₂), 2.27 (t, 3 H, J 1.8 Hz, Me), 1.56 and 1.44 (2 s, 6 H, CMe₂). Mass spectrum: m/e 213 (M⁺), 198 (M - 15), 155 (M - COMe₂), 138 (M - COMe₂ - OH), and 112 (M - COMe₂ - Ac).

Anal. Calc. for C₁₀H₁₅NO₄: C, 56.34; H, 7.04; N, 6.57. Found: C, 56.27; H, 6.83; N, 6.57.

Methyl DL-2-acetyl-5-hydroxy-4-oxopentanoate (11b). — A suspension of 9b

(4.32 g) in acetic acid (5 ml) and water (5 ml) was boiled under reflux for 1 h and monitored by using the n.m.r. signal at δ 1.4 (CMe₂). When this signal had disappeared, the solution was concentrated, and the residue was distilled to give **11b** (2.52 g, 71%), b.p. 95°/0.1 Torr, m.p. 41–43°; λ_{max}^{EtOH} 254 (ε 6.9 × 10³) and 206 nm (ε 3.1 × 10³); ν_{max}^{film} 3480, 2980, 2940, 2820, 1740, 1640–1680, 1430, 1400, 1360, 1260, 1220, 1160, 1140, 1110, 1070, 1050, and 1010 cm⁻¹. ¹H-N.m.r. data (CDCl₃): δ 4.29 (s, 2 H, H-5), 4.09 (t, 1 H, J 7 Hz, H-2), 3.73 (s, 3 H, OMe), 3.12 (bs, 1 H, OH, exchangeable with D₂O), 2.97 (dd, 2 H, ²J 3 and 7 Hz, diastereotopic H-3), and 2.34 (s, 3 H, Ac). Irradiation showed coupling of H-2 and H-3. Mass spectrum: m/e 188 (M⁺), 170 (M – H₂O), 157 (M – CH₂OH), 139 (M – H₂O – CH₂OH), 129 (M – CO₂Me), 115 (M – CH₂COCH₂OH), 99, 59 (CO₂Me), 43 (Ac), 31 (CH₂OH), and 18 (H₂O).

Anal. Calc. for $C_8H_{12}O_5$: C, 51.06; H, 6.32. Oxid. equiv. (IO₄), 188. Found: C, 51.07; H, 6.15. Oxid. equiv., 193.

1-Hydroxyhexane-2,5-dione (14b). — (a) By hydrolysis of 11b. A suspension of 11b (1.2 g) in 10% aqueous sodium hydroxide (4.3 ml) was heated to 70° for 1 h. Ether (3 × 30 ml) was added, the aqueous layer was acidified with dilute hydrochloric acid, and the product was extracted with ether (3 × 50 ml). The extracts were dried (Na₂SO₄), and concentrated under diminished pressure, and the residue was fractionated, affording 14b (0.5 g, 60%), b.p. 82–85/0.5 Torr, m.p. 51°; λ_{max}^{EtOH} 276 nm ($\varepsilon 4 \times 10^3$); ν_{max}^{film} 3460, 2980, 2900, 1710, 1695, 1405, 1385, 1350, 1170, 1150, 1060, 1000, 970, and 940 cm⁻¹. ¹H-N.m.r. data (CDCl₃): δ 3.25 (b, 1 H, exchangeable with D₂O, OH), 4.25 (bs, 2 H, H-1), 2.70 (m, 4 H, H-3,4), and 2.18 (s, 3 H, H-6). Mass spectrum: *m/e* 130 (M⁺), 113 (M – OH), 99 (M – CH₂OH), 87 (M – Ac), 73 (M – MeCOCH₂), 71 (M – COCH₂OH), 59 (COCH₂OH), 57 (MeCOCH₂), 43 (Ac), 31 (CH₂OH), and 17 (OH).

Anal. Calc. for C₆H₁₀O₃: C, 55.38; H, 7.69. Found: C, 55.57, H, 7.78.

(b) By hydrolysis of 9h. A solution of 9h (3 g) in acetic acid-water (1:1, 21 ml) was heated at 80° for 1 h. After removal of the solvent under diminished pressure, the residue was distilled, yielding 14b (0.9 g, 50%), m.p. 51°, which was identical to the product in (a).

DL-3-Methoxycarbony:I-4-oxopentanoic acid (12). — A solution of sodium periodate (2.9 g) in water (80 ml) was stirred with **11b** (2.52 g) for 15 min at room temperature. Sodium hydrogen carbonate (5 g) was then added and the mixture was extracted with ether (3 × 50 ml). The aqueous layer was acidified and extracted with ether (4 × 50 ml). The extracts were dried (Na₂SO₄), and concentrated under diminished pressure, and the residue was distilled to afford **12** (1.9 g, 51%), b.p. 114–116°/0.2 Torr; v_{max}^{film} 3560–3000, 2995, 2940, 2830, 1780, 1740, 1705, 1430, 1355, 1280, 1245, 1165, 1025, 965, and 835 cm⁻¹. ¹H-N.m.r. data (CDCl₃): δ 10.7 (bs, 1 H, CO₂H), 3.92 (t, 1 H, J 7 Hz, H-3), 3.72 (s, 3 H, OMe), 2.92 (dd, 2 H, J 7 and 2 Hz, diastereotopic H-2), and 2.31 (s, 3 H, H-5).

Anal. Calc. for C7H10O5: C, 48.27; H, 5.75. Found: C, 47.94; H, 5.98%.

The ester 12 was hydrolysed by M sodium hydroxide (30 ml) for 12 h at room temperature. The solution was acidified with dilute sulphuric acid, and the product extracted with ether (4 \times 30 ml). After removal of the solvent from the extract, levulinic acid (0.5 g) was distilled, b.p. 137–139°/10 Torr.

3-Methoxycarbonyl-2,5-dimethylfuran (10). — A solution of 9b (0.98 g) in ethyl acetate (10 ml) was hydrogenated at 100°/3 Torr for 12 h over 5% Pd/C (47 mg). The catalyst was removed, the filtrate was concentrated under diminished pressure, and the residue was distilled to yield 10 (900 mg), b.p. 40-60°/0.5 Torr; λ_{max}^{EtOH} 253 nm; ν_{max}^{film} 3100, 2980, 2900, 1720, 1625, 1590, 1440, 1390, 1370, 1280, 1240, 1205, 1135, 1090, and 1010 cm⁻¹. ¹H-N.m.r. data: δ 6.03 (s, 1 H, H-4), 3.7 (s, 3 H, OMe), 2.47 and 2.20 (2 s, 6 H, 2Me). Mass spectrum: m/e 154 (M⁺) and 139 (M – Me).

Anal. Calc. for C_gH₁₀O₃: C, 62.33; H, 6.53. Found: C, 62.54; H, 6.32.

Piperidine-catalysed reaction of 1 with ethyl acetoacetate (2a). — A mixture of 1 (29 g), 2a (29g), piperidine (6 drops), and toluene (200 ml) was stirred for 12 h at room temperature. Evolution of heat and water formation were observed. The toluene layer was removed, and concentrated under diminished pressure, and the residue was distilled to yield a mixture of unsaturated isomers (28 g, 55%), b.p. 98–102°/0.5 Torr, (see above); v_{max}^{film} 3520–3300 (enol), 3000, 2930, 2860, 1770, 1670, 1635, 1625, 1595, 1575, 1490, 1470, 1440, 1370, 1260–1200, 1150, 1100, 1050, 940, 900, 845, 800, 770, and 690 cm⁻¹. ¹H-N.m.r. data: δ 6.8 (d, 1 H, J 7 Hz, =CH, E isomer 6a), 6.68 (d, 1 H, J 7 Hz, =CH, Z isomer 6a), 3.2–5.1 (m, unresolved), 2.33 (s, 3 H, Ac, E isomer), 2.28 (s, 3 H, Ac, Z isomer), 2.18 (s, 3 H, Ac, isomer 8a), 1.98 (s, 3 H, Ac, isomer 7a), and 1.1–1.5 (m, unresolved, CMe₂ and CH₃–CH₂O groups). Signals of 9a (see below) were also observed.

Anal. Calc. for C₁₂H₁₈O₅: C, 59.50; H, 7.43. Found: C, 59.23; H, 7.43.

DL-8-Ethoxycarbonyl-2.2.7-trimethyl-1.3.6-trioxaspiro[4.4]non-7-ene (9a). Acid-catalysed cyclisation of the foregoing mixture of isomers (29 g) was carried out as described above for the formation of **9b**, using carbon tetrachloride (90 ml) and acetic acid (10 ml), to give 9a (24 g, 85%), b.p. 96-98°/0.2 Torr; λ_{max}^{EtOH} 248 nm $(\varepsilon 1.12 \times 10^4); v_{\text{max}}^{\text{film}} 2985, 2920, 2858, 1695, 1680, 1668, 1648, 1630, 1555, 1470, 1450,$ 1445, 1418, 1392, 1370, 1330, 1290, 1240, 1150, 1100, 1080, 1050, 960, and 890 cm⁻¹. ¹H-N.m.r. data (CCl₄): δ 4.23 and 3.90 (2 d, 2 H, J 9.6 Hz, dioxolane CH₇), 2.97 (q, 2 H, J 2 Hz, dihydrofuran CH₂), 2.22 (t, 3 H, J 2 Hz, Me), 1.48 and 1.43 (2 s, 6 H, CMe₂), 1.26 (t, 3 H, J 8 Hz) and 4.15 (q, 2 H, J 8 Hz) both corresponding to OEt group; (C_6H_6) : δ 4.06 and 3.61 (2 d, 2 H, J 10 Hz, CH₂), 4.11 (q, 2 H, J 7 Hz), and 1.05 (t, 3 H, J 7 Hz) both corresponding to OEt group, 3.09 (dq, 1 H, J 2.5 and 16 Hz) and 2.77 (dq, 1 H, J 2.5 and 16 Hz) both corresponding to the diastereotopic protons in dihydrofuran CH2, 2.18 (t, 3 H, J 2.5 Hz, Me), 1.52 and 1.29 (2 s, 6 H, CMe₂). Mass spectrum: m/e 242 (M⁺), 227 (M – Me), 198, 184 (M – COMe₂), 169 (184 – Me), 153 (184 – CH₂OH), 141 (184 – Ac), 139, 125 (184 – COCH₂OH), 111 (184 - CO₂Et), 73 (CO₂Et), 43 (Ac, 100%), 19 (Et), and 15 (Me).

Anal. Calc. for C₁₂H₁₈O₅: C, 59.50; H, 7.43. Found: C, 59.20; H, 7.23.

Treatment of 9a (28 g) with aqueous potassium hydroxide (100 ml), as described

above for **9b**, with recrystallisation of the product from water, gave **9h** (16 g, 64%), m.p. 116–118°.

Ethyl DL-2-acetyl-5-hydroxy-4-oxopentanoate (11a). — Hydrolysis of 9a (1.7 g) with acid, as described above for 9b, gave 11a (1.1 g, 77%), b.p. 110°/0.2 Torr; λ_{\max}^{EtOH} 254 (ε 1.45 × 10⁵) and 208 nm (ε 3.8 × 10³); ν_{\max}^{film} 3420, 2980, 2940, 2900, 1720, 1430, 1400, 1360, 1260, 1225, 1190, 1140, 1120, 1070, 1040, and 1020 cm⁻¹. ¹H-N.m.r. data (CDCl₃): δ 4.30 (s, 2 H, H-5), 4.19 (q, 2 H, J 8 Hz, OCH₂Me), 4.1 (t, 1 H, J 7 Hz, H-2), 3.82 (s, 1 H, OH, exchangeable with D₂O), 2.97 (dd, 2 H, J 3 and 7 Hz, diastereotopic H-3), 2.34 (s, 3 H, Ac), and 1.28 (t, 3 H, J 8 Hz, OCH₂CH₃). Mass spectrum: *m/e* 202 (M⁺), 184 (M - H₂O), 171 (M - CH₂OH), 157 (M - OEt), 143 (M - COCH₂OH), 129 (M - CH₂COCH₂OH), 111 (M - H₂O - CO₂Et), 73 (CH₂COCH₂OH), 59 (COCH₂OH), 43 (Ac, 100%), 31 (CH₂OH), and 18 (H₂O). *Anal.* Calc. for C₉H₁₄O₅: C, 53.41; H, 6.98. Found: C, 53.30; H, 7.24%.

Hydrolysis of 11a with base, as described above for 11b, gave 14a (48%).

Reaction of 1 with pentane-2,4-dione (2c). — This reaction was accomplished as described above for 2b, starting from 1 (15.5 g), 2c (12 g), piperidine (5 drops), and toluene (180 ml), to give a mixture of isomers 6c and 7c (8 g, 20%), b.p. 99–101°/0.2 Torr. When the reaction was carried out in ether, the yield was 52.5%. N.m.r. data indicated an almost equimolar mixture of isomers which had v_{max}^{film} 3450, 2980, 2925, 2860, 1692, 1670, 1665, 1580–1610, 1450, 1415, 1365, 1350, 1315, 1255, 1205, 1150, 1115, 1050, and 885 cm⁻¹. ¹H-N.m.r. data: α,β -unsaturated isomer 6c: δ 6.6 (d, 1 H, J 6 Hz, =CH), 4.58 (d, 2 H, J 6 Hz, dioxolane CH₂), 4.5–3.5 (m, unresolved), 2.32 (s, 3 H, Ac), 2.16 (s, 3 H, Ac), and 1.3 (6 H, CMe₂); enolic isomer 7c: δ 13.6 (s, 1 H, OH), 5.3 (t, 1 H, J 1.2 Hz, =CH), 4.3 (d, 2 H, J 1.2 Hz, dioxolane CH₂), 2.08 (s, 3 H, Ac), 2.04 (s, 3 H, enol Me), and 1.4 (6 H, CMe₂). Irradiation showed coupling between the signals at δ 5.3 and 4.3. Mass spectrum: m/e 212 (M⁺), 169 (M – Ac), 154 (M – COMe₂), 139 (154 – Me), 137 (154 – OH), 111 (154 – Ac), 95 (154 – CH₂OH), 59 (COCH₂OH), and 43 (Ac, 100%).

Anal. Calc. for C₁₁H₁₆O₄: C, 62.26; H, 7.54. Found: C, 61.98; H, 7.41.

The mixture of **6c** and **7c** (10 g) was suspended in 10% aqueous cupric acetate (90 ml) and stirred with chloroform (50 ml) with dropwise addition of ammonium hydroxide to maintain neutral pH. The chloroform solution was washed with several portions of water, dried (CaCl₂), and concentrated under diminished pressure, and the residue was recrystallised from tetrahydrofuran to give the copper salt (5.8 g, 50%), m.p. 125–127°.

Anal. Calc. for C₂₂H₃₀CuO₈: C, 54.40; H, 6.22; Cu, 13.07. Found: C, 54.31; H, 6.12; Cu, 12.92.

Isomerisation of 6c to 7c. — Lewatit S-100 resin (20 g) was partially neutralised by stirring for 3 days with aqueous sodium hydroxide (20–40 mequiv.), and then dried over calcium chloride. A solution of the mixture (8 g) of 6c and 7c in carbon tetrachloride (40 ml) was shaken with 16 g of the neutralised resin until the n.m.r. signals of 6c disappeared. The catalyst was removed and the filtrate was concentrated under diminished pressure to give 7c which gave a positive enol test with ferric chloride and had $\nu_{\text{max}}^{\text{film}}$ 3450, 2980, 2930, 2870, 1680, 1620, 1600, 1450, 1420, 1370, 1240, 1210, 1180, 1150, 1120, and 1060 cm⁻¹

Under similar conditions, after using Lewatit S-100 resin previously treated with methanol and later adding trifluoroacetic acid, 7c was isolated together with 3-acetyl-5-methoxymethyl-2-methylfuran (15, 19%), b.p. 79-81°/0.1 Torr; λ_{max}^{MeOH} 268 nm (ϵ 2.36 × 10³); ν_{max}^{film} 3100, 2980, 2920, 1670, 1550, 1360, 1230, 1080, 1050, 940, and 890 cm⁻¹. ¹H-N.m.r. data: δ 6.48 (s, 1 H, H-4), 4.25 (s, 2 H, CH₂O), 3.3 (s, 3 H, OMe), 2.57 (s, 3 H, Ac), and 2.30 (s, 3 H, Me). Mass spectrum: *m/e* 168 (M⁺), 153 (M – Me), 137 (M – OMe), 95 (M – COCH₂OMe), and 43 (Ac, 100%). *Anal.* Calc. for C₉H₁₂O₃: C, 64.28; H, 7.14. Found: C, 64.32; H, 7.26.

Anal. Calc. for $C_9 \Pi_{12} O_3$. C, 04.26; H, 7.14. Found: C, 04.32; H, 7.20

3-Acetyl-5-hydroxymethyl-2-methylfuran (5c). — The mixture (2 g) of 6c and 7c (2 g) in acetic acid-water (1:1, 4 ml) was heated at 90° for 1 h. After evaporation of solvents, the residue was distilled to yield 5c (0.98 g, 67%), b.p. 68–70°/0.1 Torr; v_{max}^{film} 3450, 2980, 2900, 1740, 1721, 1630, 1545, 1390, 1335, 1200, 1160, 1130, 1050, and 1030 cm⁻¹. ¹H-N.m.r. data (CDCl₃): δ 6.51 (s, 1 H, H-4), 4.55 (s, 2 H, CH₂O), 2.57 (s, 3 H, Ac), and 2.39 (s, 3 H, Me). Mass spectrum: *m/e* 154 (M⁺), 139 (M – Me), 123 (M – CH₂OH), 111 (M – Ac), 59 (COCH₂OH), 43 (Ac, 100%), 31 (CH₂OH), and 15 (Me).

Anal. Calc. for C₈H₁₀O₃: C, 62.33; H, 6.53. Found: C, 62.49; H, 6.50.

DL-8-Acetyl-2,2,7-trimethyl-1,3,6-trioxaspiro[4.4]non-7-ene (9c). — A solution of 7c (8 g) and trifluoroacetic acid (0.5 ml) in carbon tetrachloride (40 ml) was heated at 40° for 8 h, and then neutralised by shaking with saturated, aqueous sodium hydrogen carbonate, dried (Na₂SO₄), and concentrated under diminished pressure. The residue was distilled and afforded 9c (3.6 g, 45%), b.p. 71-73°/0.5 Torr, identical (i.r. and n.m.r.) with the product described above.

A solution of calcium hypochlorite (8 g) in warm, 60% aqueous methanol (50 ml) was treated with anhydrous potassium carbonate (7 g) and a solution of potassium hydroxide (2.25 g) in the same aqueous methanol (25 ml). After stirring for 5 min, the mixture was cooled and filtered, and the solid residue was washed with cold methanol (10 ml). Another solution of **9c** (4.5 g) in methanol (25 ml) was added with cooling (ice bath). Stirring was maintained for 6 h. A solution of sodium hydrogen sulphite (2.25 g) in water was added followed by acidification (8% hydrochloric acid). The solid which separated was recrystallised from water to give DL-8-carboxy-2,2,7-trimethyl-1,3,6-trioxaspiro[4.4]non-7-ene (**9h**; 1 g, 22%), m.p. 116-118°, which was identical (i.r. and n.m.r. spectra) with the product obtained above by base-catalysed hydrolysis of **9b** or **9a**.

Reaction of 1 with ethyl benzoylacetate (2d). — As in the above piperidinecatalysed reactions, equimolar proportions of 1 and 2d were used, but only DL-8ethoxycarbonyl-2,2-dimethyl-7-phenyl-1,3,6-trioxaspiro[4.4]non-7-ene (9d, 60%) was isolated, b.p. 157–159°/0.1 Torr. In toluene, the yield was only 45%. Compound 9d had λ_{max}^{EtOH} 246 (ε 1.19 × 10⁴) and 208 nm (ε 1.38 × 10⁴); ν_{max}^{film} 3060, 2980, 2930, 1735, 1680, 1635, 1620, 1600, 1580, 1450, 1370, 1320, 1300, 1260, 1210, 1150, 1120, 1050, and 1030 cm⁻¹. ¹H-N.m.r. data (CDCl₃): δ 7.85–7.42 (m, 5 H, Ph), 4.36 and 4.02 (2 d, 2 H, J 9 Hz, dioxolane CH₂), 4.14 (q, 2 H, J 8 Hz, OCH₂CH₃), 1.2 (t, 3 H, J 8 Hz, OCH₂CH₃), 3.22 (s, 2 H, dihydrofuran CH₂), 1.58 and 1.42 (2 s, 6 H, CMe₂). Mass spectrum: *m/e* 304 (M⁺), 289 (M - Me), 259 (M - OEt), 246 (M - COMe), 229 (246 - OH), 217 (246 - Et), 201 (246 - OEt), 169 (246 - Ph), 141 (246 - PhCO), 105 (PhCO, 100%), 77 (Ph), 59 (COCH₂OH), and 58 (COMe₂). *Anal.* Calc. for C₁₇H₂₀O₅: C, 67.10; H, 6.58. Found: C, 67.18; H, 6.77.

DL-8-Carboxy-2,2-dimethyl-7-phenyl-1,3,6-trioxaspiro[4.4]non-7-ene (9k). — This hydrolysis was accomplished as described above for 9b, using 9d (3 g, 0.1 mol), potassium hydroxide (0.67 g, 0.12 mol), ethanol (15 ml), and water (15 ml). The basic solution was washed with ether (3 × 150 ml). On acidification, the acid 9k (1.8 g, 67%) separated; m.p. 127° (from water); λ_{max}^{EtOH} 282 (ε 8.75 × 10³) and 216 nm (ε 9.58 × 10³); ν_{max}^{KBr} 3500–2950 (broad), 3050, 2980, 2920, 2850, 1650, 1630, 1620, 1580, 1570, 1545, 1460, 1425, 1350, 1270, 1250, 1225, 1180, 1110, 1070, 1045, 1030, and 670 cm⁻¹. ¹H-N.m.r. data (CDCl₃): δ 17.4 (bs, 1 H, CO₂H), 7.8–7.4 (m, 5 H, Ph), 4.37 and 4.03 (2 d, 2 H, J 10 Hz, dioxolane CH₂), 3.2 (s, 2 H, dihydrofuran CH₂), 1.57 and 1.41 (2 s, 6 H, CMe₂). Mass spectrum: *m/e* 276 (M⁺), 261 (M – Me), 218 (M – COMe₂), 201 (218 – OH), 187 (218 – CH₂OH), 173 (218 – OEt), 159 (218 – COCH₂OH), 141 (218 – Ph), 113 (218 – COPh), 105 (COPh, 100%), 77 (Ph), 59 (COCH,OH), and 58 (COMe₂).

Anal. Calc. for C₁₅H₁₆O₅: C, 65.22; H, 5.80. Found: C, 65.09; H, 5.91.

DL-8-Acetyl-2,2-dimethyl-7-phenyl-1,3,6-trioxaspiro[4.4]non-7-ene (9e). — A solution of 9k (3.35 g, 12 mmol) in anhydrous dimethoxyethane (10 ml) was treated with methyl-lithium (0.6 g) in ether (7 ml), as described above for 9h. The product was extracted with ether (3 × 100 ml) to give crude product (0.9 g, 27%) which was distilled to yield 9e (0.3 g), b.p. 130°/0.2 Torr, m.p. 56–58°; $\lambda_{max}^{CHCl_3}$ 316 nm (ε 1.92 × 10⁴); v_{max}^{film} 3040, 2970, 2950, 2818, 1635, 1620, 1605, 1590, 1575, 1560, 1540, 1440, 1425, 1370, 1350, 1340, 1270, 1230, 1210, 1125, 1100, 1070, and 1030 cm⁻¹. ¹H-N.m.r. data: (CDCl_3): δ 7.46 (m, 5 H, Ph), 4.36 and 4.03 (2 d, 2 H, J 9 Hz, dioxolane CH₂), 3.24 (s, 2 H, dihydrofuran CH₂), 1.97 (s, 3 H, Ac), 1.58 and 1.47 (2 s, 6 H, CMe₂); (C₆H₆): δ 4.15 and 3.65 (2 d, 2 H, J 9.6 Hz, dioxolane CH₂), 3.24 and 2.98 (2 d, 2 H, J 16 Hz, diastereotopic dihydrofuran CH₂), 1.84 (s, 3 H, Ac), 1.54 and 1.32 (2 s, 6 H, CMe₂).

Anal. Calc. for C₁₆H₁₈O₄: C, 70.07; H, 6.57. Found: C, 71.11; H, 6.58.

Ethyl DL-2-benzoyl-5-hydroxy-4-oxopentanoate (11d). — This hydrolysis was accomplished as described above for 9b, using 9d (2 g) and 50% aqueous acetic acid (200 ml), to give 11d (1.3 g), b.p. 88-90°/0.1 Torr; λ_{max}^{EtOH} 249 (ϵ 1.92 × 10⁴) and 210 nm (ϵ 1.74 × 10⁴); ν_{max}^{film} 3450, 3050, 2970, 2900, 1750, 1710, 1700, 1660, 1620, 1580, 1560, 1430, 1370, 1350, 1300, 1250, 1200, 1140, 1100, 1080, and 1060 cm⁻¹. ¹H-N.m.r. data: δ 8.0–7.52 (m, 5 H, Ph), 4.20 (q, 2 H, J 8 Hz, OCH₂CH₃), 1.28 (t, 3 H, J 8 Hz, OCH₂CH₃), 4.15 (t, 1 H, J 7 Hz, H-2), 3.98 (s, 1 H, OH), 3.92 (s, 2 H, H-5), and 2.70 (dd, 2 H, J 3 and 7 Hz, H-3). Mass spectrum: *m/e* 264 (M⁺), 246 (M – H₂O), 219 (M – OEt), 205 (M – COCH₂OH), 201 (M – H₂O – OEt), 191 (M – CO₂Et

or $M - CH_2COCH_2OH$, 187 (M – Ph), 159 (M – COPh), 105 (COPh), 77 (Ph), 73, 59 (COCH₂OH), 31 (CH₂OH), 18 (H₂O), and 17 (OH).

Anal. Calc. for C₁₄H₁₆O₅: C, 63.63; H, 6.06. Found: C, 63.34; H, 5.96.

4-Benzoyl-1-hydroxybutan-2-one (14d). — (a) A suspension of 9k (1.8 g) in 50% aqueous acetic acid (14 ml) was boiled under reflux for 2 h. After removal of the solvents, the residue was recrystallised from water to give 14d (0.81 g, 71%), m.p. 64–66°; λ_{max}^{EtOH} 242 nm (ε 1.31 × 10⁴); ν_{max}^{film} 3420, 3050, 2900, 2850, 2790, 1720, 1675, 1590, 1570, 1440, 1390, 1360, 1350, 1290, 1230, 1205, 1170, 1124, 1070, 1010, and 750 cm⁻¹. ¹H-N.m.r. data (CDCl₃): δ 7.8–7.48 (m, 5 H, Ph), 4.35 (s, 2 H, H-1), 3.30 and 2.80 (2 t, 4 H, J 6 Hz, H-3,4). Mass spectrum: m/e 192 (M⁺), 175 (M – OH), 161 (M – CH₂OH), 133 (M – COCH₂OH), 119 (CH₂COPh), 115 (M – Ph), 105 (COPh, 100%), 87 (M – COPh), 77 (Ph), 73 (CH₂COCH₂OH), 59 (COCH₂OH), 31 (CH₂OH), and 17 (OH).

Anal. Calc. for C₁₁H₁₂O₃: C, 69.75; H, 6.25. Found: C, 69.75; H, 6.35.

(b) A solution of 9d (6 g) in ethanol (48 ml) was mixed with a solution of sodium hydroxide (10 g) in water (48 ml). After heating at $\sim 100^{\circ}$ for 1 h, the mixture was cooled, acidified (8% hydrochloric acid), and concentrated under diminished pressure. The residue (2 g) was recrystallised from water to give 14d which was identical (i.r. and n.m.r. spectra) with the product in (a).

3-Ethoxycarbonyl-5-hydroxymethyl-2-phenylfuran (5d). — A solution of 9d (1.4 g) in carbon tetrachloride (14 ml) and trifluoroacetic acid (1 ml) was boiled under reflux for 1 h and then kept for 14 h at room temperature. After removal of the solvent under diminished pressure, the residue was distilled to give 5d (0.33 g, 30%), b.p. 68-70°/0.1 Torr; v_{max}^{film} 3500, 3060, 2980, 2935, 1790, 1740, 1685, 1655, 1640, 1625, 1595, 1450, 1410, 1370, 1330, 1265, 1200, 1150, 1095, 1030, and 685 cm⁻¹. ¹H-N.m.r. data: δ 7.70–7.50 (m, 5 H, Ph), 5.55 (s, 1 H, H-4), 4.18 (dq, 2 H, J 6 Hz, OCH₂CH₃), 3.85 (s, 2 H, CH₂O), and 1.2 (dt, 3 H, J 6 Hz, OCH₂CH₃).

Anal. Calc. for C₁₄H₁₄O₄: C, 68.29; H, 5.69. Found: C, 67.98; H, 5.40%.

Reaction of 1 with benzoylacetone (2e). — The reaction was carried out in toluene solution, as described for 2a. After removing the water produced in the reaction, the mixture was boiled under reflux for 1 h before removal of the solvent. The residue was distilled, yielding a mixture (17 g, 81% total yield) of isomers 9e and 9g, b.p. $130-132^{\circ}/0.2$ Torr.

Anal. Calc. for C₁₆H₁₈O₄: C, 70.07; H, 6.57. Found: C, 69.90; H, 6.42.

Elution of a portion (7 g) of the mixture from Kieselgel 60 (Merck, 7734) with light petroleum–ethyl ether (6:4) gave, first, DL-8-benzoyl-2,2,7-trimethyl-1,3,6trioxaspiro[4.4]non-7-ene (9g), b.p. 120°/0.2 Torr, m.p. 56°, $R_F 0.37$; $\lambda_{max}^{CHCl_3}$ 316 nm ($\varepsilon 2.8 \times 10^4$); v_{max}^{KBr} 3040, 2920, 2900, 2840, 1635, 1620, 1590, 1570, 1560, 1540, 1440, 1430, 1365, 1350, 1340, 1280, 1260, 1210, 1130, 1100, 1070, 1040, 950, 765, and 730 cm⁻¹. ¹H-N.m.r. data (CDCl₃): δ 7.45 (m, 5 H, Ph), 4.3 and 3.99 (2 d, 2 H, J 9 Hz, dioxolane CH₂), 3.20 (q, 2 H, J 1.2 Hz, dihydrofuran CH₂), 1.90 (t, 3 H, J 1.2 Hz, Me), 1.58 and 1.45 (2 s, 6 H, CMe₂).

Eluted second was DL-8-acetyl-2,2-dimethyl-7-phenyl-1,3,6-trioxaspiro[4.4]-

non-7-ene (9e, 3.2 g), R_F 0.25, b.p. 121°/0.2 Torr, m.p. 58°, which was identical (i.r. and n.m.r. spectra) with the product obtained by reaction of methyl-lithium with 9k.

The haloform reaction of 9e was carried out as described for 9c, but starting from the mixture of 9e and 9g (4 g). The second of these isomers was not affected and was removed by extraction with ether (60 ml) before acidification. The isomer 9ewas transformed into 9k which was identical (i.r. and n.m.r. spectra) with the product prepared from 9h (see above).

Reaction of 1 with methyl malonate (2f). — A solution of 1 (18 g), 2f (19 g), and piperidine (10 ml) in toluene (200 ml) was boiled for 20 h under reflux. After removal of the solvent under diminished pressure, the residue was distilled to give, first, a fraction (7.2 g), b.p. 88–92°/0.5 Torr, containing methyl (4S)-4,5-isopropylidenedioxy-2-methoxycarbonylpent-2-enoate (6f) and methyl 4,5-isopropylidenedioxy-2-methoxycarbonylpent-3-enoate (8f) (R_F 0.4 and 0.6, respectively; t.l.c., Kieselgel GF₂₅₄, methyl ether-light petroleum, 2:3).

Anal. Calc. for C₁₁H₁₆O₆: C, 54.10; H, 6.56. Found: C, 54.01; H, 6.53.

The second fraction, b.p. $103-105^{\circ}/0.5$ Torr, contained only **8f**; λ_{max}^{EtOH} 224 nm ($\varepsilon 1.68 \times 10^{+}$); v_{max}^{film} 2998, 2940, 2860, 1750, 1740, 1700, 1685, 1675, 1640, 1625, 1600, 1560, 1540, 1460, 1440, 1385, 1375, 1260, 1215, 1150, 1120, 1055, and 1020 cm⁻¹. ¹H-N.m.r. data δ 4.90 (dt, 1 H, J 10 and 5 Hz, H-3), 4.52 (m, 2 H, dioxolane CH₂), 3.68 (m, 7 H, OMe, H-2), and 1.42 (s, 6 H, CMe₂). Mass spectrum: m/e 244 (M⁺), 229 (M – Me), 185 (M – CO₂Me), and 59 (CO₂Me).

Anal. Calc. for C₁₁H₁₆O₆: C, 54.10; H, 6.56. Found: C, 53.98; H, 6.67.

A solution of the mixture (4 g) of **6f** and **8f** in carbon tetrachloride (30 ml) containing trifluoroacetic acid (0.5 ml) was boiled for 1 h under reflux. After removal of the solvent under diminished pressure, the residue was distilled to yield known^{3e} methyl *trans*-4,5-isopropylidenedioxypent-2-enoate (**16**, 1.4 g) b.p. $60-62^{\circ}/0.2$ Torr.

trans(?)-3,11-Dimethoxycarbonyl-2,10-dimethyl-1,6,9,13-tetraoxadispiro[4.2.4.-2]tetradeca-2,10-diene (17b). — A solution of 9b (3 g) and trifluoroacetic acid (1.5 ml) in carbon tetrachloride (30 ml) was boiled for 1 h under reflux under anhydrous conditions. After 12 h at room temperature, the solid (0.7 g) was collected and dried to give 17b, m.p. 128°; λ_{max}^{E1OH} 248 nm (ε 1.71 × 10⁴); ν_{max}^{KBr} 3000, 2950, 2920, 2880, 2840, 1710, 1660, 1460, 1445, 1390, 1380, 1310, 1240, 1200, 1150, 1130, 1110, 1050, 985, 965, 935, 850, and 675 cm⁻¹. ¹H-N.m.r. data: (CDCl₃): δ 4.18 and 3.69 (2 d, 4 H, J 12 Hz, H-7,14), 3.69 (s, 6 H, 2 OMe), 2.76 (q, 4 H, J 2 Hz, H-4,12), and 2.25 (t, 6 H, J 2 Hz, 2 Me). Mass spectrum m/e 340 (M⁺), 309 (M – OMe), 187 (M – 153), 170 (M/2), 153 (100%), 139 (153 – COCH₂), and 59 (CO₂Me).

Anal. Calc. for C₁₆H₂₀O₈: C, 62.34; H, 6.49. Found: C, 62.53; H, 6.60.

trans(?)-3,11-Diacetyl-2,10-dimethyl-1,6,9,13-tetraoxadispiro[4.2.4.2]tetradeca-2,10-diene (17c). — Using a method similar to that described above for 17b, but using a double proportion of trifluoroacetic acid and longer boiling under reflux (24 h), 9c (4 g) was converted into 17c (1.7 g, 46%), m.p. 119–120° (from carbon tetrachloride); $\lambda_{max}^{CHCl_3}$ 268 nm ($\varepsilon 2 \times 10^4$); v_{max}^{KBr} 2978, 2930, 1730, 1665, 1620, 1450, 1430, 1375, 1250, 1210, 1155, 1115, and 1060 cm⁻¹. ¹H-N.m.r. data (CDCl₃): δ 4.21 and 3.71 (2 d, 4 H, J 12 Hz, H-7,14), 2.8 (q, 4 H, J 1.6 Hz, H-4,12), 2.27 (t, 6 H, J 1.6 Hz, 2 Me), and 2.2 (s, 6 H, 2 COMe). Mass spectrum: m/e 308 (M⁺), 137, and 153 (M - 137 - H₂O).

Anal. Calc. for C₁₆H₂₀O₆: C, 56.47; H, 5.88. Found: C, 56.31; H, 6.02.

trans(?)-3,11-Diethoxycarbonyl-2,10-dimethyl-1,6,9,13-tetraoxadispiro[4.2.4.2]tetradeca-2,10-diene (17a). — Using a method similar to that described above for 17b, 9a was converted into 17a (62%); $\lambda_{max}^{CHCl_3}$ 248 nm (ε 1.73 × 10⁴); ν_{max}^{KBr} 2980, 2920, 2870, 1740, 1650, 1450, 1430, 1375, 1360, 1310, 1210, 1150, 1100, and 1060 cm⁻¹. ¹H-N.m.r. data (CDCl₃): δ 4.16 (q, 4 H, J 2 Hz, 2 OCH₂CH₃), 4.08 and 3.76 (2 d, 4 H, J 12 Hz, dioxane CH₂), 2.24 (t, 6 H, J 1.8 Hz, 2 Me), 2.76 (q, 4 H, J 1.8 Hz, dihydrofuran CH₂), and 1.23 (t, 6 H, J 2 Hz, 2 OCH₂CH₃).

Anal. Calc. for C₁₈H₂₄O₈: C, 58.66; H, 6.57. Found: C, 58.57; H, 6.71.

REFERENCES

- 1 P. E. PAPADAKIS, J. Org. Chem., 20 (1955) 630-638.
- 2 F. J. LOPEZ APARICIO, M. YRUELA ANTIÑOLO, AND F. GARCIA GONZALEZ, An. R. Soc. Esp. Fis. Quim., Ser. B, 54 (1958) 705-714.
- 3 (a) H. ZINNER, E. WITTEMBURG, AND G. REMBARZ, Chem. Ber., 92 (1959) 1614–1617; (b) N. K. KOCHETKOV and B. I. DMITRIEV, Chem. Ind. (London), (1962) 2147–2148; Izv. Akad. Nauk SSSR, Ser. Khim., (1962) 1262–1263; (c) F. MICHEEL AND W. MOELLER, Justus Liebigs Ann. Chem., 670 (1963) 63–68; (d) F. ALONSO CERMENO, A. M. GONZALEZ NOGAL, AND F. J. LOPEZ APARICIO, An. R. Soc. Esp. Fis. Quim., Ser. B, 68 (1972) 285–292; (e) F. J. LOPEZ APARICIO AND F. J. LOPEZ HERRERA, ibid., 72 (1976) 931–937; (f) F. J. LOPEZ APARICIO, M. GOMEZ GUILLEN, AND I. IZQUIERDO CUBERO, ibid., 72 (1976) 938–945.

⁴ F. GARCIA GONZALEZ, Adv. Carbohydr. Chem., 11 (1956) 97-143.