Convenient Syntheses of Bifunctional C_{12}-Acyclic Compounds from Cyclododecanone †

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The conversion of cyclododecanone by convenient, non-hazardous, and high-yielding reactions into a set of useful C_{12}-bifunctional intermediates is described. Baeyer–Villiger oxidation and hydrolysis give a hydroxy acid, successively converted into the bromo acid, bromo alcohol, crude bromo aldehyde, pure bromo aldehyde ethylene acetal, and pure bromo aldehyde. Preferred reagents for the transformation $CO_2H \longrightarrow CHO$ are borane–dimethyl sulphide followed by dimethyl sulphoxide–oxalyl dichloride–triethylamine.

Needing acyclic building-blocks of the type $X[CH_2]_nY$ with no contamination either from near homologues or from symmetrical compounds of the same chain length, we found the choice of pure and inexpensive starting materials limited to two—undec-10-enoic acid, derived from castor oil, and cyclododecanone (1), derived from butadiene. Choosing the latter compound, we briefly investigated oximation [1] and Beckmann rearrangement,[1,2] but found the readily obtained lactam inconvenient for further transformation, and reactions designed to give more reactive intermediates (*e.g.* cyclic imino halides) unsatisfactory. We turned to Baeyer–Villiger oxidation, but with normal peracids, *e.g.* *m*-chloroperbenzoic acid, this medium-ring ketone required reaction times of many days.[3] Trifluoroperacetic acid has the necessary higher reactivity [4] but was ruled out as being too expensive for large-scale use; permaleic acid, however, has been used with cyclo-octanone,[5] can be prepared from the anhydride and 90% hydrogen peroxide, and can be used *in situ*. This procedure was found to be convenient and effective with the C_{12}-ketone (1). However, it was considered too hazardous for repeated use on a large scale, and direct substitution of 30% peroxide was unsuccessful. Attempts to concentrate hydrogen peroxide by adding anhydrous sodium sulphate and crystallising out the hydrate failed. Use of the *in situ* method with 30% peroxide and enough maleic anhydride to react with the surplus water gave encouraging results, but the large amount of solid maleic acid which formed was inconvenient, and it proved possible to replace most of the maleic anhydride by acetic anhydride. This led to a procedure which we found to be inexpensive, convenient, and probably safe, which gave a 77% yield of reasonably pure dodecanolide (2), along with small amounts of unchanged ketone, hydroxydodecanoic acid (3a), and dodecanedioic acid (which were not worth recovering). Hydrolysis and recrystallisation gave the pure hydroxy acid (3a); this may well be the method of choice for Baeyer–Villiger oxidation of unreactive ketones.

Following literature precedent,[6] a solution of hydrogen bromide in acetic acid (prepared from the constant-boiling aqueous acid and acetic anhydride) converted the hydroxy acid into the bromo acid (4) in good yield. It did not, however, react significantly with the lactone (2), possibly for steric reasons. Other methods of converting $-CH_2OH$ into $-CH_2Br$ (*e.g.* *via* the ester of the hydroxy acid and its toluene-*p*-sulphonate treated with tetrabutylammonium bromide, or the use of triphenylphosphine and bromine, then methanol) proved much less satisfactory.

The reduction of methyl 12-bromododecanoate to the corresponding primary alcohol (lit. m.p. 28 °C) with lithium aluminium hydride has been reported.[7] In our hands both this reagent and lithium borohydride gave mixtures of 12-bromododecan-1-ol (5) and dodecan-1-ol itself, from which the bromo alcohol could not be economically separated. The latter result is consistent with recent work [8] showing that lithium alkoxyborohydrides, necessary intermediates in the $LiBH_4$ reduction of an ester, are more powerful reducing agents than the borohydride itself and can reduce alkyl halides. Borane–dimethyl sulphide, however, smoothly reduced the free acid to 12-bromododecan-1-ol (5), m.p. 31—32 °C, in good yield, without any evidence of attack on the CH_2Br group either by hydride or by dimethyl sulphide.[9]

The oxidation of the bromo alcohol to the corresponding aldehyde (6) proved difficult. Chromic acid on silica gel,[10] pyridinium dichromate,[11] and pyridinium chlorochromate [12] all gave variable (occasionally satisfactory) yields of products which were less than completely pure and difficult to purify, which autoxidised in air, and self-condensed with little provocation. Probably the bromine atom as well as the hydroxy group were oxidised by Cr^{VI},[13] pyridine from the pyridinium salts may have reacted with the CH_2Br group to give alkylpyridinium salts, and paramagnetic precipitates and traces of hydrogen bromide may have catalysed autoxidation, self-condensation, and oligomerisation processes. Oxidation with oxalyl dichloride–dimethyl sulphoxide–triethylamine [14] gave much better results, crude products being formed quantitatively, free from starting materials, and were much more stable.

The crude aldehyde prepared in this way contained a little unchanged alcohol (i) when any of the reagents, or the apparatus, was not carefully dried; (ii) when the oxalyl dichloride had not been redistilled; and (iii) when a magnetic stirrer, inadequate for the scale of the experiment, was used. When the ethyl bromide was omitted, reaction products obtained from the aldehyde contained impurities in which Cl replaced Br. These were reduced to negligible proportions when ethyl bromide (6 mol equiv.) was added to the solvent, and (presumably) pre-empted *ca.* 95% of such minor reactions. However, our crude aldehyde also contained non-polar contaminants, including malodorous sulphur compounds which were highly undesirable because catalytic hydrogenation was contemplated at a later stage. They no doubt included the known [14] by-product RCH_2OCH_2SMe (R = 11-bromoundecyl), but the ester RCH_2OCOR (carbonyl band at 1 730 cm^{-1} but no C(=O)–H stretching band) and the acetal $RCH(OCH_2R)_2$ were also present. The latter was identified by elemental analysis and by the recognition of the molecular ion (triplet at *m/z* 508, 510, 512) of the vinyl ether, its pyrolysis product. Acetals and esters have not previously been reported as by-products in Swern oxidations.

† Considered Part 1 of a series entitled 'Studies on the Synthesis of Linear Aliphatic Compounds.'

Table. ^{13}C- and ^{1}H-Chemical shifts of unperturbed terminal groups, $\overset{\text{ipso}}{X}\overset{\alpha}{C}H_2\overset{\beta}{C}H_2\overset{\gamma}{C}H_2CH_2-$ [a]

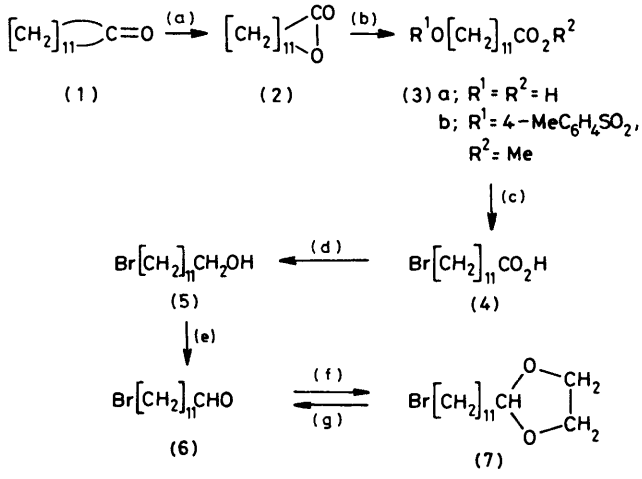
	δ_C (p.p.m.)				δ_H			
X	ipso	α	β	γ	ipso	α	β	γ
H	—	14.0	22.8	32.3	—	1.27	—	—
Br	—	33.82—34.02	32.72—32.96	28.06—28.29	—	3.39	1.85	1.41
OH	—	63.0	32.9	25.9	—	3.61	1.55	—
CO_2H	180.5	34.11	24.6	—	—	2.34	1.63	—
CHO	202	43.5	21.7	—	9.74	2.41	1.6	—
$(O_2C_2H_4)$	64.77—64.84	104.51—104.82	24.02—24.14	33.92	3.90	4.84	1.61	—

[a] Methylene groups more remote from X than $CH_2(\gamma)$ had chemical shifts inseparable at 50.1 Hz (^{13}C), 200 MHz (^{1}H) from internal CH_2 groups at δ_C 29.5 p.p.m., δ_H 1.27.

Purification of the crude bromoaldehyde by chromatography on silica was tedious on the scale needed, and on distillation at 130 °C and 0.1 mmHg it oligeromised to a solid, analogous to paraldehyde or metaldehyde. On treatment with ethylene glycol and toluene-*p*-sulphonic acid, however, it gave a stable acetal (7) which could be purified without difficulty. The crude acetal contained some unchanged aldehyde. Three techniques avoided this: (i) the reaction was carried out by adsorbing the glycol–acid mixture (20%) on dried silica gel, and allowing the aldehyde to percolate down a column, thus using a cascade process to drive the equilibrium to completion; (ii) trimethyl orthoformate was added to the reaction mixture [15] to react with the water formed in acetalisation; and (iii) trimethyl orthoformate was first treated with the ethylene glycol and acid catalyst, and heated until the methanol, formed in an interchange reaction, had been volatilised. Method (i) gave a pure product in 80% yield; method (ii) a product containing *ca.* 7% of the dimethyl acetal (easily estimated by n.m.r.) in 77% yield; and method (iii), devised to deal with this problem, a pure product in 89% yield. This last technique may be the method of choice for the preparation of dioxolans from reactive aldehydes. The expected orthoformate was obtained from the glycol–trimethyl orthoformate mixture, but there was no advantage in isolating it.

Regeneration of aldehydes from ethylene acetals has not been much studied, and most literature methods gave low yields or products showing signs of self-condensation (i.r. band at 1 690 cm^{-1}). Conia's technique [16] for ethylene ketals was modified by carrying out the reaction in a chromatographic column, so that the usual advantage of a cascade process was obtained, and by substituting 25% aqueous toluene-*p*-sulphonic acid for the sulphuric acid—this led to less darkening of the mixtures and higher recoveries. The aldehyde was obtained in *ca.* quantitative yield, but removal of the last trace of solvent caused some deterioration, as judged by the appearance of a band at 1 690 cm^{-1} (CH=CRCHO). The aldehyde could conveniently be used in methylene dichloride solution. When an attempt was made to deprotect the acetal in diethyl ether–light petroleum mixtures, characteristic acetal bands at 1 135 and 1 145 cm^{-1} were seen in the i.r. spectrum of the aldehyde product—these bands provide a sensitive test for such contamination. Our route is summarised in the Scheme.

During this and subsequent work with C_{12}-bifunctional compounds, ^{1}H- and ^{13}C-n.m.r. spectra were needed for structural confirmation. The chain length is enough to permit carbon atoms 1, 2, or 3 atoms away from the functional groups to be regarded as not otherwise perturbed. We therefore list (Table) the values observed, with a range where five or more observations are available, as these data may be helpful in similar work. Except for the ethylene acetal group the assignments of ^{13}C chemical shifts follow from less precise (and less completely unperturbed) data in the literature; for $Br[CH_2]_{11}\overset{\dagger}{C}(H)OC_2H_4\overset{\dagger}{O}$ the α, β, and γ methylene groups showed $Eu(fod)_3$* shifts, at comparable concentrations, of 21.58, 12.2, and 4.4 p.p.m., respectively.



Scheme. *Reagents:* (a) 30% H_2O_2, Ac_2O, maleic anhydride, CH_2Cl_2; (b) KOH, MeOH, $\overset{+}{H}$; (c) HBr (aq.), Ac_2O; (d) BH_3–Me_2S, Et_2O; (e) $(COCl)_2$, Me_2SO, CH_2Cl_2, EtBr, NEt_3; (f) $(HOCH_2)_2$, $C_7H_7SO_3H$, $(\overset{\dagger}{O}CH_2CH_2\overset{\dagger}{O}CHOCH_2)_2$; (g) H_2O, SiO_2, $C_7H_7SO_3H$, CH_2Cl_2–light petroleum

Experimental

Silica gel was the 60—120 mesh grade; molecular sieves were Aldrich 8—12 mesh, having a pore diameter of 4 Å. Reduced-pressure evaporations were performed on a rotary evaporator.

Lactone (2) *of* 12-*Hydroxydodecanoic Acid.*—Methylene dichloride (1.6 l) and acetic anhydride (1.25 l) were stirred in a 5-l flask fitted with a double-surface reflux condenser and an overhead stirrer and cooled externally (ice–water) while 30% hydrogen peroxide (1 l) was added. After 1 h maleic anhydride (1 kg) was added, the mixture was cooled and stirred for 1 h, and then the cooling-bath was removed, when the temperature rose during 1.5 h and the mixture began to reflux. External cooling was resumed when needed to moderate the reaction.

* $Eu(fod)_3$ = Europium tris-(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dionate).

When little more heat was evolved, cyclododecanone (1) (250 g) was added; this did not greatly increase the rate of heating, and when spontaneous refluxing ceased a heating mantle was used to maintain the mixture at its b.p. for 15 h. The mixture was then cooled and the separated maleic acid was filtered off. The filtrate was washed in turn with water (3 × 600 ml), an aqueous solution containing 10% each of potassium hydroxide and sodium sulphite (2 × 300 ml), then water (600 ml); tests for peroxide were now negative. After being dried (Na_2SO_4) the filtrate was evaporated to give the lactone (2) (210.4 g, 77%); when potassium carbonate, rather than potassium hydroxide, was used for washing, the crude lactone contained a pungent contaminant, probably peracetic acid. (Isolation of the acidic fraction gave a mixture, difficult to separate, of 12-hydroxydodecanoic and dodecanedioic acid.)

12-*Hydroxydodecanoic Acid* (3a).—The foregoing lactone was added to a solution of potassium hydroxide (150 g) in methanol (800 ml) and the mixture was heated under reflux for 1 h. Most of the solvent was then removed on a rotary evaporator. Water (2 l) was added and the solution was extracted with diethyl ether (2 × 400 ml). The aqueous layer was acidified (concentrated HCl) and the precipitated acid was collected, dried *in vacuo*, and recrystallised from acetone–light petroleum (b.p. 60—80 °C) to afford the acid (3a) (185.8 g, 63% from cyclododecanone), m.p. 84 °C (lit.,[17] 84—85 °C). [Isolation of the neutral fraction gave a small amount of cyclododecanone (1).]

12-*Bromododecanoic Acid* (4).—Acetic anhydride (700 ml) was added cautiously to 47% aqueous hydrobromic acid (190 ml), followed by the hydroxy acid (3a) (185.8 g), and the mixture was heated at 100 °C for 3 h. The solvents were removed, first at 15 mmHg, then at 1 mmHg, on a rotary evaporator. The dark residue was dissolved in hot, light petroleum (b.p. 40—60 °C) and the solution was treated with animal charcoal and filtered, when the bromo acid (4) (212.1 g, second crop 5.0 g; total yield 91%) separated out, m.p. 52—54 °C (lit.,[18] 52 °C).

12-*Bromododecan*-1-*ol* (5).—A solution of 12-bromododecanoic acid (4) (217.1 g) in sodium-dried diethyl ether (1 l) was stirred under nitrogen in a flame-dried 2-l flask in a fume chamber. Borane–dimethyl sulphide (100 ml) was added during 3 h with ice-cooling. When hydrogen evolution had ceased the mixture was heated under reflux for 1 h. Water (200 ml) was then added, cautiously at first with external ice-cooling, when a white precipitate formed; this dissolved as more water (800 ml) was added. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 200 ml). The organic phase was washed in turn with water (300 ml), 10% aqueous sodium carbonate (2 × 300 ml), and water (200 ml), and was then dried (Na_2SO_4). Evaporation and recrystallisation of the residue from light petroleum (b.p. 30—40 °C) gave the alcohol (5) (188.2 g, second crop 6.0 g; total yield 94%), m.p. 31—32 °C (lit.,[7] 28 °C) (Found: C, 54.35; H, 9.75; Br, 30.1. Calc. for $C_{12}H_{25}BrO$: C, 54.35; H, 9.5; Br, 30.15%).

Although otherwise apparently pure, the material thus prepared sometimes retained an unpleasant odour. This was removed, without any effect on other properties, by brief (30 min) treatment with an equal weight of glacial acetic acid and one tenth of the weight of 30% hydrogen peroxide, followed by isolation of the neutral fraction and recrystallisation.

Crude 12-*Bromododecanal* (6).—(*a*) To a flame-dried 2-l, 3-necked flask fitted with overhead stirrer, pressure-compensated dropping funnel, and nitrogen inlet, methylene dichloride (300 ml; distilled from P_4O_{10} and stored over molecular sieves), ethyl bromide (60 ml; stored over molecular sieves), and oxalyl dichloride (38.5 ml; recently distilled) were added. The mixture was stirred and cooled to −70 °C while a solution of dimethyl sulphoxide (67.5 ml; redistilled at 0.04 mmHg from calcium hydride and kept over molecular sieves) in dry methylene dichloride (100 ml) was added during 30 min. The mixture was stirred for a further 30 min, then a solution of 12-bromododecan-1-ol (5) (80 g) in dry methylene dichloride (200 ml) was added during 20 min, and the mixture was then stirred for a further 40 min when a white precipitate formed. Freshly distilled triethylamine (225 ml) was then added during 5 min and the cooling bath was removed; the mixture warmed to nearly room temperature during 1 h. Water (390 ml) was added rapidly and the mixture was stirred for a further 15 min. The layers were separated and the aqueous phase was extracted with methylene dichloride (150 ml). The extract was washed in turn with 1.5M hydrochloric acid (2 × 200 ml), 10% aqueous potassium carbonate (2 × 200 ml), and water (100 ml) and was dried (Na_2SO_4). Evaporation of a small aliquot gave a residue which, in carbon tetrachloride, showed no alcohol absorption at 3 600 cm^{-1}, but did show bands at 2 940, 2 870, 2 820, 2 720, and 1 730 cm^{-1}—the fourth peak [C(O)−H str.] being stronger than the third.

Chromatographic purification at this stage showed the presence of (i) the 12-bromododecyl acetal of the desired aldehyde, (ii) 12-bromododecyl 12-bromododecanoate (band at 1 730 cm^{-1} but none at 2 720 cm^{-1}), and (iii) a malodorous compound believed to be the derived 12-(methylthiomethyl) ether. Evaporation to small volume from large-scale preparations resulted in self-condensation (band at 1 690 cm^{-1}); distillation at *ca.* 130 °C and 0.1 mmHg gave a liquid which rapidly oligomerised to a solid which showed no C=O absorption. We normally converted this crude aldehyde into the ethylene acetal (7) (see below).

(*b*—*not optimised*).[19] A stirred mixture of 12-bromododecan-1-ol (5) (10.0 g), triethylamine (25 g), and dry dimethyl sulphoxide (50 ml) was treated with a solution of pyridine–sulphur trioxide adduct (18.1 g) in dry dimethyl sulphoxide (50 ml) added during 15 min under nitrogen; the flask was externally cooled to maintain an internal temperature of 25 °C. After 2 h water (100 ml) and 2M aqueous hydrochloric acid (to make the final pH 4—5) were added. The mixture was extracted with light petroleum (b.p. 30—40 °C) (2 × 100 ml) and the extracts were washed in turn with 10% aqueous potassium carbonate (3 × 25 ml) and water (50 ml) and were dried. Evaporation of an aliquot and i.r. analysis of the residue showed the crude aldehyde to contain perhaps 5—10% of unchanged alcohol, while conversion into the ethylene acetal [method (*a*) below] and crystallisation indicated an overall yield from the alcohol of 58%. However, malodorous by-products were less evident in the crude product prepared by this method, as has previously been stated.[19]

12-*Bromododecanal Ethylene Acetal* (7).—*Method* (*a*) Ethylene glycol (160 ml), trimethyl orthoformate (40 ml), and toluene-*p*-sulphonic acid (0.8 g) were heated under reflux for 1 h and the mixture was then warmed and evaporated under reduced pressure. A methylene dichloride solution of crude 12-bromododecanal (6) [*ca.* 700 ml; from bromododecanol (80 g), method (*a*) above] was evaporated to *ca.* 350 ml, and the glycol–orthoformate mixture was added. Evaporation was continued under reduced pressure until no volatile material remained, and the mixture was then stirred under nitrogen at 20 °C for 16 h. Light petroleum (b.p. 30—40 °C; 250 ml) and 10% aqueous potassium carbonate (50 ml) were added to the shaken mixture and the layers were separated. The organic

layer was washed with 10% aqueous potassium carbonate (50 ml) and dried (Na_2SO_4 plus a little Na_2CO_3). Evaporation, during which some methyl mercaptan was evolved, gave a residue (89.7 g) which was crystallised three times from light petroleum (b.p. 30—40 °C; 600 ml) at −70 °C to give the *acetal* (7) (82.8 g, 89% from the alcohol), m.p. 22.5—24 °C (Found: C, 55.0; H, 8.9; Br, 26.05. $C_{14}H_{27}BrO_2$ requires C, 54.75; H, 8.85; Br, 26.0%); $\nu_{max.}$ (CCl_4) 1 145, 1 135, 1 040, and 940 cm^{-1}. Contamination with the corresponding dimethyl acetal was shown by the filling in of the minimum at 1 085 cm^{-1}, and was evident when the method of ref. 15 was used; the dimethyl acetal content could be estimated from its ^1H n.m.r. signal at δ 3.28.

(*b*). A mixture of silica gel (200 g), ethylene glycol (40 g), toluene-*p*-sulphonic acid (4 g), and methanol (50 ml) was evaporated under reduced pressure, first at room temperature and then at 50 °C, until all the methanol had evaporated and the glycol–acid mixture was evenly distributed on the silica, giving a free-flowing powder. This was loaded into a chromatography column, and crude 12-bromododecanal (6) [from bromododecanol (20 g), method (*a*) above] was added as a solution in a 1 : 3 mixture of methylene dichloride and light petroleum (b.p. 30—40 °C). Elution was continued with the same solvent. The eluate (*ca.* 500 ml) was evaporated to 120 ml, washed with 10% aqueous potassium carbonate (2 × 20 ml), dried (Na_2SO_4 + Na_2CO_3), and evaporated to give a residue (20.24 g, 87%), m.p. 22—24 °C. Crystallisation at −70 °C gave the acetal (18.55 g), m.p. 23—24 °C, and this m.p. was unchanged after distillation, b.p. 134—136 °C at 0.05 mmHg (17.0 g recovery).

12-*Bromododecanal by Hydrolysis of the Acetal* (7).—Aqueous toluene-*p*-sulphonic acid (25%; 60 ml) was added to silica gel (600 g) suspended in a mixture of light petroleum (b.p. 30—40 °C) and methylene dichloride (3 : 1), and the mixture was stirred vigorously, then placed in a chromatography column. A solution of the acetal (7) (41.3 g) in light petroleum (b.p. 30—40 °C) (50 ml) was added, and the column was eluted slowly with the 3 : 1 mixture until an aliquot was found (i.r. spectrum) to contain the required aldehyde (*ca.* 1 h, 600 ml eluant). Elution was then continued rapidly with pure methylene dichloride until further fractions contained negligible amounts (*ca.* 1.5 h, 3 l). The eluates were combined and evaporated at 25 °C at 15 mmHg to give the aldehyde (33.8 g, 96%), pure except for a very little methylene dichloride. The *dinitrophenylhydrazone* had m.p. 100—102 °C (Found: C, 48.7; H, 6.35; Br, 17.35; N, 12.3. $C_{18}H_{27}BrN_4O_4$ requires C, 48.85; H, 6.1; Br, 17.35; N, 12.65%).

Toluene-p-*sulphonate* (3a) *of Methyl* 12-*Hydroxydodecanoate*.—Methyl 12-hydroxydodecanoate,[20] m.p. 33 °C, was prepared from the hydroxy acid (3a) (11 g), methanol (35 ml), and concentrated sulphuric acid at room temperature during 16 h. The ester (7.57 g) was added to a mixture of toluene-*p*-sulphonyl chloride (6.89 g) and dry pyridine (20 ml). After 1 h water was added and the neutral product was isolated, to give the *toluene*-p-*sulphonate* (3b) (9.89 g, 78%), m.p. 40—41 °C (Found: C, 63.0; H, 8.25. $C_{20}H_{32}O_3S$ requires C, 62.45; H, 8.4%). On treatment with tetrabutylammonium bromide in tetrahydrofuran it gave the corresponding bromo ester, m.p. 7 °C (lit.,[21] 7 °C) in good yield.

Ethylene Glycol Orthoformate *.—Ethylene glycol (93 g), trimethyl orthoformate (106 g), and toluene-*p*-sulphonic acid (0.5 g) were heated under reflux for 3 h, then under reduced pressure to remove methanol. Diethyl ether (50 ml) was added to the residue and the mixture was washed in turn with 10% aqueous potassium carbonate (2 × 20 ml) and water (2 × 20 ml) and dried ($MgSO_4$). Evaporation gave a residue (5 g, 2%) which, on distillation (Kugelrohr) at 140 °C at 0.25 mmHg gave the *ortho-ester* (Found: C, 46.7; H, 7.05. $C_8H_{14}O_6$ requires C, 46.6; H, 6.85%). The low yield is presumably a consequence of high solubility in water; however, the ^1H- and ^{13}C-n.m.r. spectra were in full agreement with the formula.

* 2,2′-Ethylenedioxydi-1,3-dioxolan.

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