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Note

The 4-oxovaleryl and 3-benzoylpropionyl groups for the protection of hydroxyl functions

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Because of the mild conditions for its removal, the 3-benzoylpropionyl group has potential for the protection of hydroxyl groups The reaction of simple esters of 3-benzoylpropionic acid with hydrazine hydrate–acetic acid–pyridine to give 4,5-dihydro-6-phenylpyridazine is long known[1], but the reaction was not exploited until recently applied[2,3] to nucleosides Subsequently, Gagnaire and his co-workers[4] used 3-benzoylpropionic anhydride to prepare D-glucose derivatives as part of a study of the synthesis of oligosaccharides on solid supports Letsinger *et al*[2,3] employed the free acid with dicyclohexylcarbodiimide (DCC) as the condensing agent Polymer supports incorporating the 3-benzoylpropionyl group have been used for the synthesis of oligonucleolides[5,6]. The 3-benzoylpropionyl group is stable under the conditions necessary for the removal of dimethyl-*tert*-butylsilyl groups[7]

The 3-acetylpropionyl (4-oxovaleryl) group should be as effective as its benzoyl analogue, and the associated reagents less expensive Apparently, the 3-benzoylpropionyl group has not been used for blocking polyhydroxylic systems

We have investigated the synthesis of 3-acylpropionyl derivatives of 1,2 5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**) and of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**3**) by three methods involving (*1*) the DCC procedure[2,3], (*2*) prior formation of the pentachlorophenyl esters, and (*3*) the anhydride procedure[4]. Method (*1*) has also been used for the synthesis of some sucrose derivatives The DCC method[2,3] was complicated by the difficulty in separating the products derived from carbohydrate derivatives of low molecular weight from *N*,*N*′-dicyclohexylurea Moreover, the product yields were not good (*cf* ref 4) 1,2 5,6-Di-*O*-isopropylidene-3-*O*-(4-oxovaleryl)-α-D-glucofuranose (**4**), and mono- and di-benzoylpropionyl derivatives of **3** required extensive chromatography for purification. Attempts to

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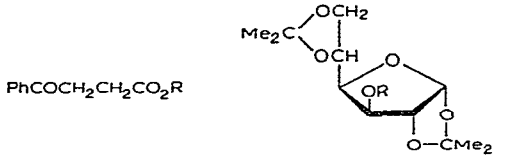
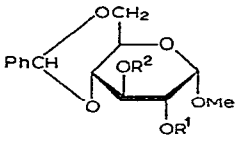
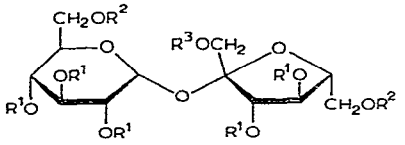
prepare the 3-benzoylpropionyl derivative of **2** and 4-oxovalerates of **3** failed because of purification problems



2 R = H
4 R = $MeCOCH_2CH_2CO$



3 $R^1 = R^2 = H$
5 $R^1 = R^2 = PhCOCH_2CH_2CO$
6 $R^1 = H$ $R^2 = PhCOCH_2CH_2CO$
11 $R^1 = H$, $R^2 = MeCOCH_2CH_2CO$
12 $R^1 = R^2 = MeCOCH_2CH_2CO$



7 $R^1 = Bz$, $R^2 = R^3 = H$
8 $R^1 = Bz$, $R^2 = R^3 = PhCOCH_2CH_2CO$
9 $R^1 = R^3 = Bz$ $R^2 = H$
10 $R^1 = R^3 = Bz$ $R^2 = PhCOCH_2CH_2CO$

The structure (**6**) of the mono-ester of **3** followed from its p m r. spectrum, which showed a triplet at τ 4 66 ($J_{2,3} = J_{3,4} = 9$ Hz) for H-3, moved down field from its position in **3** by acylation of HO-3 H-2 would be expected to give a quartet in the same region because of vicinal *ax* and *eq* hydrogens Such a signal (τ 5 1) was present in the di-ester **5** in addition to that for H-3 For **6**, only the signal (τ 5 18) for H-1 occurred between that for H-3 and τ 5 65

Treatment of sucrose pentabenzoate[8] (**7**) and sucrose hexabenzoate[9] (**9**) with 3-benzoylpropionic acid–pyridine–dicyclohexylcarbodiimide at room temperature gave, after chromatography, 1′,6,6′-tri-*O*-(3-benzoylpropionyl)sucrose pentabenzoate (**8**, 43%) and 6,6′-di-*O*-(3-benzoylpropionyl)sucrose hexabenzoate (**10**, 41%), respectively

Side reactions in the condensation of amino acids using DCC may be reduced by adding trichlorophenol[10,11] Such an addition had no effect in the corresponding reactions of **2** and **3** A similar modification is to use the pentachlorophenyl ester of an amino acid[12] A transesterification reaction was achieved using **2**, pentachlorophenyl 3-benzoylpropionate, and imidazole in dichloromethane, which yielded 3-*O*-(3-benzoylpropionyl)-1,2 5,6-di-*O*-isopropylidene-α-D-glucofuranose

The anhydride method[4] is the simplest and best-yielding 4-Oxovaleric anhydride was prepared by a method similar to that for 3-benzoylpropionic anhydride[4], and it converted **3** into a mono- (**11**) and a di-ester (**12**) The minor product **11** was shown to be an O-3 derivative by p m r data Selective substitution at O-3 in **3** is in agreement with work on acetylation by Jeanloz and Jeanloz[13]

The 3-acylpropionyl esters were cleaved by hydrazine hydrate in pyridine–acetic acid

EXPERIMENTAL

All rotations are for solutions in chloroform, and n m r spectra for solutions in chloroform-*d* unless otherwise stated

1,2 5,6-Di-O-isopropylidene-3-O-(4-oxovaleryl)-α-D-glucofuranose (**4**) — A solution of 1,2 5,6-di-*O*-isopropylidene-α-D-glucofuranose (0 86 g) in anhydrous, redistilled pyridine (20 ml) was stirred with DCC (2 68 g) and 4-oxovaleric (levulinic) acid (1 15 g) at room temperature During 16 h, the mixture became dark brown Water (6 ml) was added, and stirring was continued for a further 8 h The filtered mixture was partitioned between chloroform and water, and the organic phase was washed with dilute hydrochloric acid, dilute aqueous sodium hydrogen carbonate, and water, then dried, and evaporated *in vacuo* The residue was purified by p l c (using ether and then chloroform) and then recrystallised from light petroleum to give **4** (0 51 g, 43%), m p 78 5–80 0°, $[\alpha]_D^{25}$ −38° (*c* 1 195) (Found C, 57 25, H, 7 2 $C_{17}H_{26}O_8$ calc C, 57 0, H, 7 3%) N m r data τ 4 2 (*d*, $J_{1,2}$ 3 5 Hz, H-1), 4 9 (*broad*, H-3), 5 6 (*d*, H-2), 5 9–6 3 (*m*, H-4,5,6,6'), 7 2–7 7 (*m*, $2CH_2$), 7 9 (*s*, Me), 8 6–8 9 (4*s*, 4Me)

Reaction of **3** *with 3-benzoylpropionic acid and DCC* — Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**3**, 5 g), 3-benzoylpropionic acid (13 g), and DCC (15 g) were dissolved in anhydrous, redistilled pyridine (100 ml), and the mixture was left overnight Water (13 ml) was added, and the mixture was stirred for 5 h, then filtered, and concentrated *in vacuo*, and toluene was distilled from the residue *N,N'*-Dicyclohexylurea was partially removed at this stage by repeated dissolution in ethyl acetate, filtration, and evaporation *in vacuo* The product was crystallised from ether–light petroleum, with seeding, to yield the crude 2,3-diester **5** (2 2 g) The mother liquors were evaporated and the residue was eluted from silica gel with ether–light petroleum (1 2) to yield more **5** (0 5 g), and the 3-ester **6** (0 7 g)

Methyl 2,3-di-*O*-(3-benzoylpropionyl)-4,6-*O*-benzylidene-α-D-glucopyranoside (**5**) had m p 197–198° (from ether–light petroleum), $[\alpha]_D^{25}$ +28° (*c* 1) (Found C, 67 2, H, 6 0 $C_{34}H_{34}O_{10}$ calc C, 67 8, H, 5 7%) N m r data τ 2 2–2 7 (*m*, 3Ph), 4 4 (*t*, $J_{2,3} = J_{3,4} = 8$ Hz, H-3), 5 05 (*q*, H-2), 5 1 (*d*, $J_{1,2}$ 4 Hz, H-1), 5 7 (*m*, H-6*e*'), 6 0–6 5 (*m*, H-4,5,6*a*), 6 6 (*s*, OMe), 6 7 (2*t*, $2CH_2$), 7 2 (2*t*, $2CH_2$)

Methyl 3-*O*-(3-benzoylpropionyl)-4,6-*O*-benzylidene-α-D-glucopyranoside (**6**) had m p 162–163°, $[\alpha]_D^{25}$ +89° (*c* 0 55) (Found C, 65 8, H, 5 8 $C_{24}H_{26}O_8$ calc C, 65 2, H, 5 9%) N m r data τ 2 2–2 7 (*m*, 2Ph), 4 5 (*s*, PhC*H*), 4 6 (*t*, $J_{2,3} = J_{3,4} =$ 9 Hz, H-3), 5 2 (*d*, $J_{1,2}$ 4 Hz, H-1), 5 7 (*q*, H-6*e*), 6 0–6 5 (*m*, H-2,4,5,6*a*), 6 5 (*s*, MeO), 6 7 (*t*, CH_2), 7 2 (*t*, CH_2)

2,3,3',4,4'-Penta-O-benzoyl-1',6,6'-tri-O-(3-benzoylpropionyl)sucrose (**8**) — A solution of **7** (3 g), 3-benzoylpropionic acid (4 5 g), and DCC (5 g) in pyridine was stirred at room temperature for 20 h Water (1 ml) was added to the reaction mixture and stirring was continued for 5 h The mixture was filtered and concentrated to afford a semi-crystalline residue Ethyl acetate (30 ml) was added, insoluble material was filtered off, and the filtrate was concentrated This procedure was repeated until

no solid residue was formed on concentration T l c. (ether–light petroleum, 4 1) then showed a fast-moving, major product Elution from a column of silica gel (100 g), using ether–light petroleum (1.1), gave **8** (2 g, 43%), m p 68–70° (from ethanol), $[\alpha]_D^{25}$ +22° (*c* 2 3) (Found C, 68 7, H, 5 0 $C_{77}H_{66}O_{22}$ calc · C, 68 85, H, 4 9%) N m r data· τ 3 95 (*d*, $J_{1,2}$ 3 5 Hz, H-1), 4 63 (*q*, $J_{2,3}$ 10 0 Hz, H-2), 3 92 (*t*, $J_{3,4}$ 10 0 Hz, H-3), 4 4 (*t*, $J_{4\,5}$ 10 0 Hz, H-4), 4 06–4 14 (H-3′ and H-4′), 6 57–6 82 (4 protons, propionate), 7 06–7 38 (4 protons, propionate), 1.75–2 74 (8Ph)

*1′,2,3,3′,4,4′-Hexa-*O*-benzoyl-6,6′-di-*O*-(3-benzoylpropionyl)sucrose* (**10**) — A solution of **9** (500 mg), 3-benzoylpropionic acid (800 mg), and DCC (900 mg) in pyridine was stirred at room temperature for 24 h. Water (2 ml) was added, and the mixture was stirred for 5 h and then worked up as described previously to give a syrup T l c (ether–light petroleum, 4:1) showed a fast-moving, major product Elution from a column of silica gel (50 g), using ether–light petroleum (1 1), gave **10** (270 mg, 41%), m p 72–74° (from ethanol), $[\alpha]_D^{25}$ +19° (*c* 0 97) (Found C, 68 8; H, 5.0 $C_{74}H_{62}O_{21}$ calc · C, 69 05; H, 4 8%) N m r data τ 3 9 (*d*, $J_{1,2}$ 3 5 Hz, H-1), 4 61 (*q*, $J_{2\,3}$ 10 0 Hz, H-2), 3 84 (*t*, $J_{3,4}$ 10 0 Hz, H-3), 4 4 (*t*, $J_{4,5}$ 10 0 Hz, H-4), 4 0 (*d*, $J_{3,4}$ 6 0 Hz, H-3′), 4 05 (*t*, $J_{4',5'}$ 6 0 Hz, H-4′), 6 6–6 78 (2 protons, propionate), 7 06–7 25 (2 protons, propionate), 1.76–2 95 (8Ph)

Reactions of 4-oxovaleric anhydride — (*a*) *1,2 5,6-Di-*O*-isopropylidene-α-*D*-glucofuranose.* Levulinic acid (15 6 g) was dissolved in anhydrous ether (300 ml), and DCC (15 5 g) was added, the urea began to precipitate almost immediately After 18 h, the reaction mixture was filtered, the precipitate was washed with ether, and the filtrate and washings were evaporated *in vacuo* The residue, a pale-yellow oil, which crystallised slowly, was a mixture of the free acid and its anhydride uncontaminated (i r, n m r) by DCC or *N,N′*-dicyclohexylurea

1,2 5,6-Di-*O*-isopropylidene-α-D-glucopyranose (1 g) was dissolved in anhydrous, redistilled pyridine (50 ml), and crude 4-oxovaleric anhydride (1.1 g) was added After 24 h, the reaction mixture was evaporated *in vacuo*, a solution of the residue in chloroform was washed with aqueous sodium hydrogen carbonate and water, and then evaporated, and toluene was distilled from the residue to remove traces of pyridine. A solution of the residue in ether was stirred for 2 h with activated charcoal Crystallisation of the purified product from light petroleum gave **4** (93%), identical to the product described above.

(*b*) *Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside* The crude product obtained by using the method described in (*a*) was subjected to p l c (ether, 2 developments) The di-ester was washed with aqueous sodium hydrogen carbonate to remove free acid. Methyl 4,6-*O*-benzylidene-2,3-di-*O*-(4-oxovaleryl)-α-D-glucopyranoside was obtained as a syrup (30%), $[\alpha]_D^{25}$ +31° (*c* 1) (Found C, 60 3, H, 6.7. $C_{24}H_{30}O_{10}$ calc.: C, 60 2, H, 6 3%) N m r data τ 2 4–2 8 (*m*, Ph), 4 5 (*s*, PhC*H*), 4 5 (*t*, $J_{2\,3} = J_{3,4} = 7$ Hz, H-3), 5 1 (*q*, H-2), 5.2 (*d*, $J_{1,2}$ 4 Hz, H-1), 5 5–6 5 (*m*, H-4,5,6*a*,6*e*), 6.6 (*s*, MeO), 7 3 (*m*, $2CH_2$), 7 4 (*m*, $2CH_2$), 7 8 (*s*, 2AcO)

Methyl 4,6-*O*-benzylidene-3-*O*-(4-oxovaleryl)-α-D-glucopyranoside (8%) had m p. 145–146°, $[\alpha]_D^{25}$ +93 5° (*c* 1) (Found. C, 60 3, H, 6.5. $C_{19}H_{24}O_8$ calc.: C, 60.0,

H, 6 4%) N m r data τ 2 4–2 8 (*m*, Ph), 4 5 (*s*, PhC*H*), 4 65 (*t*, $J_{2,3} = J_{3,4} = 7$ 5 Hz, H-3), 5 2 (*d*, $J_{1,2}$ 3 5 Hz, H-1), 5 5–6 5 (*m*, H-2,4,5,6*a*,6*e*), 6 6 (*s*, MeO), 7 3 (*m*, $2CH_2$), 7 8 (*s*, AcO)

Pentachlorophenyl 3-benzoylpropionate — Pentachlorophenol (2 67 g), benzoylpropionic acid (1 78 g), and DCC (2 06 g) were dissolved in dry dichloromethane (150 ml) Precipitation of *N,N'*-dicyclohexylurea commenced almost immediately, and the reaction mixture was stirred overnight The precipitate was collected and washed, and the filtrate and washings were evaporated *in vacuo* The residue was repeatedly dissolved in ethyl acetate, and the solution filtered and evaporated to remove the urea Column chromatography (silica gel, chloroform) gave the title compound (3 6 g, 85%), m p 121–122° (Found C, 45 2, H, 2 15, Cl, 41 3 $C_{16}H_9Cl_5O_3$ calc C, 45 1, H, 2 1, Cl, 41 6%)

1,2 5,6-Di-O-isopropylidene-α-D-glucofuranose 3-(3-benzoylpropionate) — A solution of the glucose derivative (2 6 g), pentachlorophenyl 3-benzoylpropionate (4 27 g), and imidazole (3 4 g) in dry dichloromethane was stirred for 2 h A 10% excess of the ester was then added, and stirring was continued overnight The filtered mixture was washed with ice-cold, aqueous sodium hydrogen carbonate, washed with water, and dried The title product, when separated from starting material by p l c, was obtained as a syrup (24%), $[\alpha]_D^{25}$ −29° (*c* 1 1) (Found C, 63 4, H, 6 5 $C_{22}H_{28}O_8$ calc C, 62 8, H, 6 7%) N m r data τ 2 0–2 8 (*m*, Ph), 4 1 (*d*, H-1), 4 7 (*d*, H-3), 5 5 (*d*, H-2), 5 6–6 3 (*m*, H-4,5,6,6'), 6 7 (*m*, CH_2), 7 3 (*m*, CH_2), 8 6–8 9 (4*s*, 4Me)

Removal of 4-oxovalerate groups — To a solution of the derivative (0 5 mmole) in pyridine–acetic acid (4 1, 1 5 ml) one drop of hydrazine hydrate (99%) was added The solution was stirred at room temperature and then evaporated, and the product was isolated by recrystallisation or by chromatography The following reaction times and yields were observed **4**, 16 h (93%), **5**, 16 h (74%), **8**, 3 5 h (95%), **10**, 3 5 h (96%), **11**, 16 h (93%), **12**, 16 h (74%)

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