Reaction of Chlorosulphonyl Isocyanate with Ethyl 4,6-Di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside: a Reinvestigation

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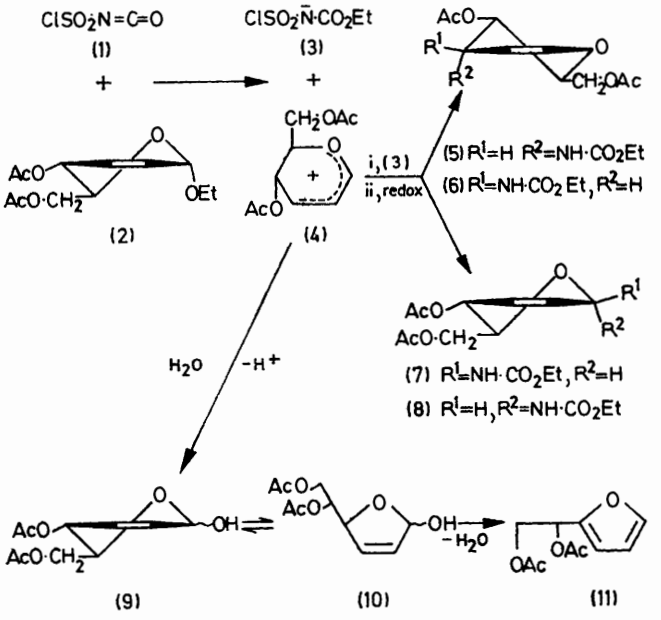
The minor products of the reaction of chlorosulphonyl isocyanate with a hex-2-enopyranoside in ether and in acetonitrile include a 3-alkoxycarbonylamino-3-deoxy-allal, 2-(D-*glycero*-1.2-diacetoxyethyl)furan, two hex-2-enopyranosylamines, and two C–C linked disaccharide derivatives. Reaction mechanisms are discussed.

A REPORT [1,†] that the reaction of chlorosulphonyl isocyanate (CSI) (1) with ethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (2) in ether gave not only the previously described [2] amino-glucal (6), but also a trace of the epimeric 4,6-di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-3-ethoxycarbonylamino-D-*ribo*-hex-1-enitol-(4,6-di-*O*-acetyl-3-deoxy-3-ethoxycarbonylamino-D-allal) (5) has prompted us to reinvestigate the reaction. It has also been reported [1] that the reaction in acetonitrile proceeds very quickly and that the glucal (6) can be isolated in good yield by recrystallization.



We have confirmed that the reaction of compound (2) with CSI in ether yields a mixture from which the glucal (6) and eight minor products can be separated by column chromatography. Owing to the difficulties in separation the yields of the minor products could not be determined accurately.

The first compound eluted was 2-(D-*glycero*-1,2-diacetoxyethyl)furan (11).[3] Then followed in succession: starting material (2); an unidentified oil in very low yield; the previously described major product (6); 4,6-di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-3-ethoxycarbonylamino-D-*ribo*-hex-1-enitol (5); 4,6-di-*O*-acetyl-2,3-dideoxy-*N*-ethoxycarbonyl-β-D-*erythro*-hex-2-enopyranosylamine (7) and its α-anomer (8); 4,6-di-*O*-acetyl-2,3-dideoxy-αβ-D-*erythro*-hex-2-enopyranose (9);[2b,4] and 5,6-di-*O*-acetyl-2,3-dideoxy-αβ-D-*erythro*-hex-2-enofuranose (10).

Compounds (5), (7), and (8) were identified mainly from their analytical and i.r. and n.m.r. spectral properties. Optical rotation measurements [5] were used to determine the anomeric configurations of compounds (7) and (8).

The i.r. spectrum of compound (10) showed peaks at 3535 and 3455 (OH) and 1730 cm^{-1} (CO) and the n.m.r. spectrum revealed that the molecule contained two acetyl groups and eight other protons. When D_2O was added to the solution the n.m.r. spectrum slowly changed until it was identical with that of the furan (11). This loss of a molecule of water from compound (10) is probably catalysed by traces of acid in the solvent mixture.

In agreement with a previous report,[1] the reaction between the hex-2-enopyranoside (2) and CSI proceeded more quickly in acetonitrile than in ether, to give an essentially similar product mixture, but containing two additional minor components: 4,6-di-*O*-acetyl-2,3-dideoxy-2-*C*-(4,6-di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-β-D-*erythro*-hex-2-enitol-1-yl)-*N*-ethoxycarbonyl-α-D-*erythro*-

† We thank Dr. Russell for his gift of a sample of the allal (5) and for some of his personal notes.

[1] A. B. Russell, personal communication.

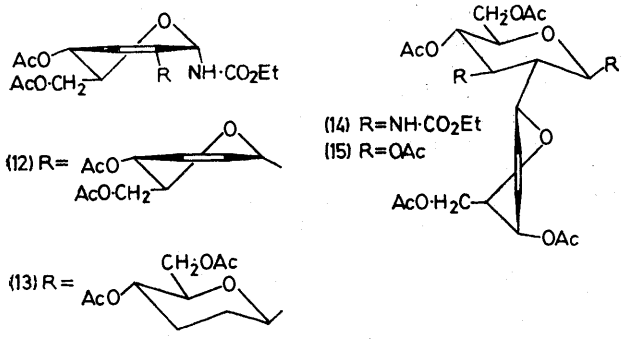
[2] (*a*) A. Jordaan and G. J. Lourens, *Chem. Comm.*, 1971, 581; (*b*) R. H. Hall, A. Jordaan, and G. J. Lourens, *J.C.S. Perkin I*, 1973, 38.

[3] (*a*) D. M. Ciment and R. J. Ferrier, *J. Chem. Soc.* (*C*), 1966, 441; (*b*) R. J. Ferrier, *Adv. Carbohydrate Chem.*, 1969, **24**, 199.

[4] B. Helferich, *Adv. Carbohydrate Chem.*, 1952, **7**, 209.

[5] J. F. Stoddart, 'Stereochemistry of Carbohydrates,' Wiley–Interscience, New York, 1971, p. 147.

hex-2-enopyranosylamine (12) and 4,6-di-*O*-acetyl-2,3-dideoxy-2-*C*-(4,6-di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-α-D-*erythro*-hex-2-enitol-1-yl)-3-ethoxycarbonylamino-*N*-ethoxycarbonyl-β-D-glucopyranosylamine (14).



The n.m.r. spectrum of compound (12) indicated the presence of four acetyl groups, one ethoxycarbonylamino-group, and showed a characteristic signal [6] for two vinyl protons. The rest of the spectrum consisted of a broadened singlet, three doublets, and a six-proton multiplet. One of the doublets collapsed to a singlet on addition of D_2O and triethylamine. The large values of $J_{4,5}$ and $J_{4',5'}$ clearly showed that both rings adopt the $^{O}H_5$ conformation in solution. It was also inferred from these large coupling constants that the rings are linked between C-1′ and -2 and not C-1′ and -3. 2,3-Dideoxy-hex-2-enopyranosides with bulky substituents at C-3 are unknown but because of the $A^{1,2}$ effect [7] it seems reasonable that the role of the substituent on C-3 will be similar to the known [8] role of a bulky substituent on C-2 in determining ring conformation and configuration at allylic positions in 2,3-dideoxy-hex-2-enopyranosides. Had the two rings been linked between C-1′ and -3 and not C-1′ and -2 the least strained conformation would have the allylic group at C-4 quasiaxial and not quasiequatorial as seen from the $J_{4,5}$ value. Owing to the $A^{1,2}$ effect the ethoxycarbonylamino-substituent on C-1 must be quasiaxial, *i.e.* the unsaturated glycosamine is the α-anomer.

The $^{O}H_5$ conformation of the nitrogen-free monosaccharide unit in compound (12) indicated that the anomeric configuration of the unit is β. A Dreiding model of compound (12) shows that an α-configuration introduces strain.

Catalytic hydrogenation of compound (12) gave a dihydro-derivative (13) which, as expected [9] for a derivative bearing a bulky group on C-2, could not be further hydrogenated. The n.m.r. spectrum of compound (13) shows that the 2′,3′-olefinic bond had been reduced and the large $J_{4,5}$ value indicated that the unsaturated ring remained in the $^{O}H_5$ conformation.

N.m.r. spectra of compound (14) were run in [^{2}H]-chloroform and [$^2H_6$]dimethyl sulphoxide and spin–spin decoupling experiments similar to those described by Ferrier and Prasad [10] were used for analysis of the spectra. The structure and conformation of compound (14) are analogous to those of compound (15), which is obtained on treating tri-*O*-acetyl-D-glucal with boron trifluoride,[10] iodine,[11] or CSI,[2] *i.e.* the unsaturated ring adopts the $^{O}H_5$ conformation. A Dreiding model confirms that this is the preferred conformation.

The formation of compounds (6)—(11) can be rationalised in terms of initial production of the stable carbocation (4) and the anionic species (3). Attack by (3) at C-3 or -1 of (4) gives compounds (5)—(8). Compounds (9)—(11) are probably formed from the carbocation (4) by a pathway analogous to that proposed [12] to explain the products of the hydrolysis of 3,6-anhydro-D-glucal.

A mechanism involving ion separation to give the carbocation (4) is preferred to an isomerization mechanism [10,13] which would involve allylic rearrangement reactions of glucal and galactal compounds in the unfavoured $^{5}H_4$ conformation. We have found that the n.m.r. spectrum of tri-*O*-acetyl-D-glucal in [$^2H_6$]dimethyl sulphoxide at temperatures as high as 120° shows only the presence of a $^{4}H_5$ conformer. In reactions like those of tri-*O*-acetyl-D-galactal with boiling acetic acid,[3] tri-*O*-acetyl-D-glucal with boron trifloride in benzene, and tri-*O*-acetyl-D-glucal and similar compounds with hydrogen bromide in acetic acid,[14] carbocations such as (4) are therefore probably the most important intermediates.

In acetonitrile the formation of compounds (12) and (14) can be explained by mechanisms involving attack by the ion (4) on compound (6) or (8). A solvent of high dielectric constant such as acetonitrile would be expected to stabilise the ionic intermediate (4) and should, as was found, contribute to a cleaner and faster reaction than that with ether as solvent.

EXPERIMENTAL

T.l.c. and column chromatography were performed with silica gel (Merck GF_{254}) (100 g of silica gel per g of residue for column separations). M.p.s were determined with a hot-stage apparatus. I.r. spectra were measured with a Perkin-Elmer 257 spectrophotometer and optical rotations were taken for solutions in chloroform with a Bendix-NPL automatic polarimeter type 143 (*c* 1·0 ± 0·3). N.m.r. spectra were recorded with a Varian HA-100 instrument (tetramethylsilane as internal standard) and mass spectra with an A.E.I. MS9 spectrometer by direct insertion.

Reaction of Ethyl 4,6-*Di*-O-*acetyl*-2,3-*dideoxy*-α-D-erythro-*hex*-2-*enopyranoside* (2) *with CSI* (1) *in Ether*.—The reaction was carried out as described previously; [2b] identical

[6] R. J. Ferrier and N. Prasad, *J. Chem. Soc.* (*C*), 1969, 570.
[7] F. Johnson, *Chem. Rev.*, 1968, **68**, 375.
[8] R. J. Ferrier and G. H. Sankey, *J. Chem. Soc.* (*C*), 1966, 2345.
[9] N. Pravdic, B. Zidovec, I. Franjic, and H. G. Fletcher, *Croat. Chem. Acta*, 1973, **45**, 343.
[10] R. J. Ferrier and N. Prasad, *J. Chem. Soc.* (*C*), 1969, 581.
[11] I. Szczerek, J. S. Jewell, R. G. S. Richie, W. A. Szarek, and J. K. N. Jones, *Carbohydrate Res.*, 1972, **22**, 163.
[12] J. S. Brimacombe, I. Da'Aboul, and L. C. N. Tucker, *Carbohydrate Res.*, 1971, **19**, 276.
[13] R. J. Ferrier, N. Prasad, and G. H. Sankey, *J. Chem. Soc.* (*C*), 1968, 974.
[14] T. Maki and S. Tejima, *Chem. and Pharm. Bull.* (*Japan*), 1968, **16**. 2242.

work-up gave a thick oil (*ca.* 5 g). T.l.c. [200 mm plate with ethyl acetate–hexane (1 : 1) an eluant] showed the presence of eight clearly identifiable fractions with R_F 0·85, 0·79, 0·76, 0·69, 0·65, 0·59, 0·53, and 0·42.

Column chromatography (same eluant as for t.l.c.) first gave an oil, which was distilled under vacuum to give an oil identical (t.l.c. and mass and i.r. spectra) with authentic 2-(D-*glycero*-1,2-diacetoxyethyl)furan (11).[3]

The second component eluted was starting material (2) and the third component, obtained in very low yield, could not be identified.

The fractions eluted next (R_F 0·69) contained pure compound (6) in high yield and then a mixture of mainly compound (6) and a second slightly slower moving component (5). From this mixture most of the amino-glucal (6) was removed by crystallization from acetone–hexane and the mixture of compounds (6) and (5) which was recovered from the mother liquors was rechromatographed twice, first with the same eluant as before and then with chloroform–diethyl ether (1 : 1) to give a pure oil which slowly crystallized. Recrystallization from ether–hexane gave 4,6-*di*-O-*acetyl*-1,5-*anhydro*-2,3-*dideoxy*-3-*ethoxycarbonylamino*-D-ribo-*hex*-1-*enitol* (5), m.p. 75—76°, $[\alpha]_D^{21}$ +175°, $\nu_{max.}$ ($CHCl_3$) 3445 (NH), 1730 (CO), and 1650 cm^{-1} (vinyl ether), *m/e* 302 ($M^+ + 1$), τ ($CDCl_3$) 3·57 (1H, d, $J_{1.2}$ 6 Hz, H-1), 4·93 (1H, q, $J_{4.5}$ 10, $J_{4.3}$ 4 Hz, H-4), 5·20 (1H, t, $J_{2.1}$ 6, $J_{2.3}$ 6 Hz, H-2), 5·34br (1H, d, $J_{NH,3}$ 8 Hz, disappears on addition of D_2O, NH), 5·54 (1H, q, $J_{3,4}$ 4, $J_{3,NH}$ 8 Hz, simplifies on addition of D_2O, H-3), 5·66—5·70 (2H, m, H-6,6′), *ca.* 5·87—6·04 (1H, m, H-5), 5·91 (2H, q, $OCH_2{\cdot}CH_3$), 7·92 (3H, s, OAc), and 8·74 (3H, t, $OCH_2{\cdot}CH_3$) (Found: C, 51·7; H, 6·5; N, 4·7. $C_{13}H_{19}NO_7$ requires C, 51·8; H, 6·4; N, 4·7%).

Work-up of the next set of fractions (R_F 0·65) gave a solid which on recrystallization from ethyl acetate–hexane gave 4,6-*di*-O-*acetyl*-2,3-*dideoxy*-N-*ethoxycarbonyl*-β-D-erythro-*hex*-2-*enopyranosylamine* (7) as needles, m.p. 106°, $[\alpha]_D^{21}$ +98°, $\nu_{max.}$ ($CHCl_3$) 3440 (NH) and 1730 cm^{-1} (CO), *m/e* 259 ($M^+ - CH_3CO_2$), τ [$(CD_3)_2SO$] 1·97br (1H, d, $J_{NH,1}$ 10 Hz, disappears on addition of D_2O, NH), 4·10 (2H, s with satellites, H-2,3), 4·46 (1H, q, $J_{1.NH}$ 10, *J ca.* 2·5 Hz, simplifies on addition of D_2O, H-1), 4·84 (1H, q, $J_{4.5}$ 8, *J ca.* 3 Hz, H-4), 5·83—6·23 (5H, m, H-5,6,6′, $OCH_2{\cdot}CH_3$), 7·96 (3H, s, OAc), 7·98 (3H, s, OAc), and 8·83 (3H, t, $OCH_2{\cdot}CH_3$) (Found: C, 51·5; H, 6·5; N, 4·6. $C_{13}H_{19}NO_7$ requires C, 51·8; H, 6·4; N, 4·7%).

The fractions eluted next (R_F 0·59) yielded a solid which on recrystallization from ethyl acetate–hexane gave 4,6-*di*-O-*acetyl*-2,3-*dideoxy*-N-*ethoxycarbonyl*-α-D-erythro-*hex*-2-*enopyranosylamine* (8) as needles, m.p. 94—95°, $[\alpha]_D^{21}$ +114°, $\nu_{max.}$ ($CHCl_3$) 3440 (NH) and 1730 cm^{-1} (CO), *m/e* 259 ($M^+ - CH_3CO_2$), τ [$(CD_3)_2SO$] 1·76br (1H, d, $J_{NH.1}$ 10 Hz, disappears on addition of D_2O, NH), 4·18 (2H, s with satellites, H-2,3), 4·53br (1H, d, $J_{1,NH}$10, *J ca.* 2 Hz, simplifies on addition of D_2O, H-1), 4·88br (1H, d, $J_{4.5}$ 8, *J* 2 Hz, H-4), 5·86—6·20 (5H, m, H-5,6,6′, $OCH_2{\cdot}CH_3$), 7·95 (3H, s, OAc), 8·00 (3H, s, OAc), and 8·84 (3H, t, $OCH_2{\cdot}CH_3$) (Found: C, 52·1; H, 6·7; N, 4·6. $C_{13}H_{19}NO_7$ requires C, 51·8; H, 6·4; N, 4·7%).

The last fractions contained a mixture of two compounds (R_F 0·53 and 0·42) which was separated by chromatography with ethyl acetate–hexane (3 : 1) as eluant. The compound eluted first was identical (i.r., mass, and n.m.r. spectra and t.l.c.) with the previously described compound (9);[2b,5] the other component of the mixture, obtained as an oil, was 5,6-*di*-O-*acetyl*-2,3-*dideoxy*-αβ-D-erythro-*hex*-2-*enofuranose* (10), $\nu_{max.}$ ($CHCl_3$) 3565 and 3440 (OH) and 1730 cm^{-1} (CO), *m/e* 187 ($M^+ - CH_2CO - H$), τ ($CDCl_3$) 3·83—4·13 (3H, m, H-2,3,5), 4·82—5·23 (2H, m, H-1,4), and 5·44—6·00 (3H, m, H-6,6′, OH). The spectrum slowly changes on addition of D_2O to give that of (11) after 24 h.

Reaction of the Hex-2-enopyranoside (2) *with CSI* (1) *in Acetonitrile.*—The reaction was carried out as described [2b] except that acetonitrile was used as solvent and the reaction time was shortened to 90 min. Work-up gave an oil (*ca.* 5 g) which slowly solidified. From this oil three successive crops of crystals, identical with authentic compound (6), were obtained by crystallization from ether. The next three crops of crystals were mixtures of compounds (6) and (14). From these mixtures compound (6) was removed by washing with ether to leave a solid which crystallized from ethyl acetate–hexane as needles of 4,6-*di*-O-*acetyl*-2,3-*dideoxy*-2-C-(4,6-*di*-O-*acetyl*-1,5-*anhydro*-2,3-*dideoxy*-α-D-erythro-*hex*-2-*enitol*-1-*yl*)-3-*ethoxycarbonylamino*-N-*ethoxycarbonyl*-β-D-*glucopyranosylamine* (14), m.p. 162·5—164°, $[\alpha]_D^{21}$ +70°, $\nu_{max.}$ ($CHCl_3$) 3420 (NH) and 1730 cm^{-1} (CO), *m/e* 542 ($M^+ - CH_3CO_2H$), τ ($CDCl_3$) 4·08 (2H, s with satellites, H-2′,3′), 4·49 (1H, d, $J_{NH.1}$ 10 Hz, disappears on addition of D_2O and Et_3N, NH), 4·82 (1H, t, $J_{1,NH}$ *ca.* 10, $J_{1.2}$ *ca.* 9 Hz, simplifies on addition of D_2O and Et_3N, H-1), 4·95 (1H, d, $J_{NH.3}$ 9 Hz), disappears on addition of D_2O, NH), 5·04 (1H, t, $J_{4.3}$ 9, $J_{4.5}$ 9 Hz, H-4), 5·14br (1H, s, $W_{\frac{1}{2}}$ *ca.* 7 Hz, H-4′), 5·55br (1H, s, $W_{\frac{1}{2}}$ *ca.* 7 Hz, H-1′), 5·65—6·40 (11H, m, simplifies on addition of D_2O and Et_3N, H-3,5,6,6′,5′,6″,6‴,2 × $OCH_2{\cdot}CH_3$), *ca.* 7·9—8·0 (1H, partly hidden by OAc signals, H-2), 7·92 (6H, s, 2 × OAc), 7·96 (6H, s, 2 × OAc), and 8·79 (6H, t, 2 × $OCH_2{\cdot}CH_3$). The spectrum in $(CD_3)_2SO$ was similar but with the NH signals downfield (τ 2·26 and 2·84) and two clearly defined broadened signals at 3·95 (1H, d, $J_{2′,3′}$ 10 Hz, H-2′) and 4·35 (1H, d, $J_{3′,2′}$ 10, $J_{3′,4′}$ *ca.* 4, $J_{3′,1′}$ *ca.* 2 Hz, H-3′) which were amenable to decoupling experiments [10] (Found: C, 51·6; H, 6·2; N, 4·9. $C_{26}H_{38}N_2O_{14}$ requires C, 51·8; H, 6·4; N, 4·7%).

The mother liquors from the crystallization of compounds (6) and (14) were combined; on removal of the solvent an oil was obtained. Chromatography with ethyl acetate–hexane (3 : 2) as eluant gave a solid which was recrystallized from ethyl acetate–hexane to give 4,6-*di*-O-*acetyl*-2,3-*dideoxy*-2-C-(4,6-*di*-O-*acetyl*-1,5-*anhydro*-2,3-*dideoxy*-β-D-erythro-*hex*-2-*enitol*-1-*yl*)-N-*ethoxycarbonyl*-α-D-erythro-*hex*-2-*enopyranosylamine* (12) as needles, m.p. 158—160°, $[\alpha]_D^{20}$ +45°, $\nu_{max.}$ ($CHCl_3$) 3435 (NH) and 1730 cm^{-1} (CO), *m/e* 454 ($M^+ - CH_3CO_2$), τ ($CDCl_3$) 3·98—4·28 (5H, m, simplifies on addition of D_2O, H-1,3,2′,3′, NH), 4·62br (1H, d, $J_{4.5 \text{ or } 4′,5′}$ 9 Hz, H-4 or 4′), 4·78br (1H, d, $J_{4.5 \text{ or } 4′,5′}$ 8 Hz, H-4 or 4′), 5·30br (1H, s, $W_{\frac{1}{2}}$ *ca.* 5 Hz, H-1′), 5·64—6·37 (8H, m, H-5,6,6′,5′,6″,6‴, $OCH_2{\cdot}CH_3$), 7·90 (3H, s, OAc), 7·93 (3H, s, OAc), and 8·75 (3H, t, $OCH_2{\cdot}CH_3$). The spectrum in $(CD_3)_2SO$ was similar but with τ 1·68 (1H, d, $J_{NH.1}$ 8, disappears on addition of D_2O, NH), 3·92—4·10 (2H, m, H-2′,3′), 4·29br (1H, s, $W_{\frac{1}{2}}$ *ca.* 5 Hz, H-3), 4·39br (1H, d, $J_{1.NH}$ 8 Hz, simplifies on addition of D_2O, H-1), and 4·84br (2H, t, $J_{4.5}$ *ca.* 8, $J_{4′,5′}$ *ca.* 8 Hz, H-4,4′) (Found: C, 53·7; H, 6·0; N, 2·7. $C_{23}H_{31}NO_{12}$ requires C, 53·8; H, 6·1; N, 2·7%).

Catalytic Hydrogenation of Compound (12).—Compound (12) in benzene over palladium–charcoal (10%) absorbed 1 mol. equiv. of hydrogen. Work-up and recrystallization from ethyl acetate–hexane gave 4,6-*di*-O-*acetyl*-2,3-*dideoxy*-

2-C-(4,6-*di*-O-*acetyl*-1,5-*anhydro*-2,3-*dideoxy*-β-D-erythro-*hexitol*-1-*yl*)-N-*ethoxycarbonyl*-α-D-erythro-*hex*-2-*enopyranosylamine* (13) as needles, m.p. 121—122°, $[\alpha]_D^{21}$ +79°, $\nu_{max.}$ ($CHCl_3$) 3330 (NH) and 1730 cm^{-1} (CO), *m/e* 473 ($M^+ - CH_2CO$), τ [$(CD_3)_2SO$] 1·77 (1H, d, $J_{NH.1}$ 9 Hz, disappears on addition of D_2O, NH), 4·17br (1H, s, $J_{3.4}$ 1·5 Hz, $W_{\frac{1}{2}}$ *ca.* 5·5 Hz, H-3), 4·48br (1H, d, $J_{1,NH}$ 8 Hz, simplifies to a singlet with D_2O, $W_{\frac{1}{2}}$ *ca.* 5 Hz, H-1), 4·76br (1H, d, $J_{4.5}$ 8, $J_{4,3}$ 1·5 Hz, H-4), 5·43br (1H, $W_{\frac{1}{2}}$ 1·7 Hz, H-4′), 5·66—6·54 (9H, m, H-5,6,6′,1′,5′,6″,6‴, OCH_2·CH_3), 7·79—8·10 (4H, m, H-2,3,2′,3′), 7·97 (6H, s, 2 × OAc), 8·00 (6H, s, 2 × OAc), and 8·84 (3H, t, OCH_2·CH_3). The spectra in [^{2}H]chloroform and [$^2H_6$]acetone were similar but with the NH signal upfield (Found: C, 53·5; H, 6·4; N, 2·8. $C_{23}H_{33}NO_{12}$ requires C, 53·6; H, 6·5; N, 2·7%).

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