Note

6-Deoxy-6-isocyanato-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose and some derivatives

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Acetylenic carbamates of the type **1**, some of which display anti-viral activity, represent a new type of antitumour agent[1,2]. For antitumour activity, R^1 and R^2 in **1** must be aryl groups; where R^1 and R^2 are alkyl groups, the compounds may have hypnotic properties[1].

Activity within a series of structurally related compounds often correlates with the partition coefficient[3], and in seeking compounds of reduced lipophilic character the synthesis of derivatives of **1** was undertaken where R^3 was a sugar residue. Although these particular compounds were not obtained, a series of carbamates was synthesised and has been reported[4].

Since a convenient route to carbamates involves the reaction of alcohols with isocyanates, the carbohydrate primary isocyanate **2** was selected and synthesised by treatment of 6-amino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose hydrochloride with phosgene, essentially by the method of Jochims and Seelinger[5].

The isocyanate **2** reacted readily with ethanol to give the corresponding carbamate **3**. However, reaction of **2** with 1,1-diphenyl-2-propyn-1-ol[6] yielded only the urea derivative **5**; the formation of a type **1** product was not detected. Urea derivatives are frequently produced in the reaction of isocyanates with alcohols, and presumably the reaction of **2** with 1,1-diphenyl-2-propyn-1-ol yields a urea derivative because of steric hindrance (bulky isocyanate, tertiary alcohol). Thus, a related primary alcohol, propargyl alcohol (2-propyn-1-ol), reacted readily with **2** to give the carbamate **4**. Removal of the isopropylidene protecting groups from the sugar by resin hydrolysis gave the water-soluble carbamate **8** which was devoid of hypnotic and antitumour activity.

The isocyanate **2** reacted readily with cyclohexylamine and *n*-butylamine to give the urea derivatives **6** and **7**.

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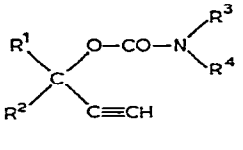
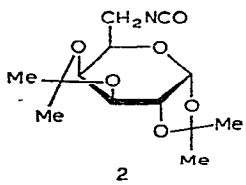


1



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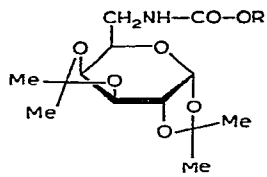
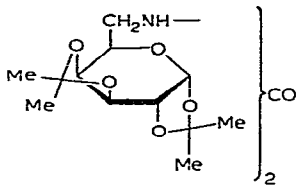


3 R = Et
4 R = CH≡C–CH$_2$



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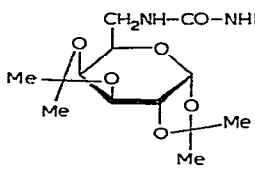
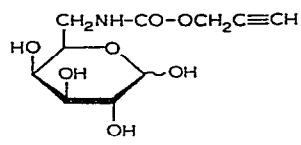


6 R = C_6H_{11}
7 R = n-C_4H_9



8

EXPERIMENTAL

Melting points are corrected. Optical rotations were determined with a Perkin–Elmer 141 polarimeter on 1–2% solutions in chloroform unless stated otherwise. N. m. r. spectra were obtained by using a Perkin–Elmer R-10 spectrometer. The following abbreviations are used: *s* singlet, *d* doublet, *q* quartet, *m*, multiplet. Light petroleum refers to the fraction b.p. 60–80°.

*6-Deoxy-6-isocyanato-1,2:3,4-di-*O*-isopropylidene-α-*D*-galactopyranose* (**2**). — 6-Amino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose hydrochloride (m.p. 230° dec.) was prepared by passing dry hydrogen chloride through a solution of the free amine[7] in dry ether; the crystalline product was collected by filtration and dried over phosphorus pentaoxide.

Dry phosgene was passed into a suspension of the hydrochloride (5.6 g) in boiling xylene until dissolution occurred (5–6 h). The solution was then purged of phosgene and hydrogen chloride by a stream of nitrogen, and concentrated, and the residue was distilled to give **2** (3.64 g, 69%), b.p. 119–121°/0.4 mmHg, $[\alpha]_D^{30}$ −42° (benzene), ν_{max}^{liquid} 2250 (N=C) and 1740 cm^{-1} (C=O) (Found: C, 54.9; H, 6.9; N, 5.1. $C_{13}H_{19}NO_6$ calc.: C, 54.7; H, 6.7; N, 4.9%). N.m.r. data (deuteriochloroform, internal tetramethylsilane): τ 4.45 (*d*, $J_{1,2}$ 5.5 Hz, H-1), 5.4 (*q*, $J_{2,3}$ 2.5, $J_{3,4}$ 7.5 Hz, H-3), 5.65 (*q*, $J_{4,5}$ 2.2 Hz, H-4), 5.75 (*m*, H-2), 6.2 (*m*, H-5), 6.55 (*m*, H-6), 6.65 (*m*, *H*-6'), 8.5, 8.6, 8.7(×2) (*s*, 4Me).

*6-Carbonylamino derivatives of 6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-*D*-galacto-pyranose.* — (*a*) A solution of the isocyanate **2** (0.1 g) in ethanol (5 ml) and triethylamine (0.1 ml) was stored overnight at room temperature and then concentrated. Recrystallisation of the residue from light petroleum gave 6-deoxy-6-ethoxycarbonylamino-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**3**, 0.11 g, 95%), m.p. 80–81°, $[\alpha]_D^{30}$ −30°, ν_{max}^{Nujol} 3400 (N–H) and 1720 cm^{-1} (carbamate C=O) (Found: C, 54.5; H, 7.3; N, 4.6. $C_{15}H_{25}NO_7$ calc.: C, 54.4; H, 7.5; N, 4.2%).

Compound **3** was also obtained by treatment of 6-amino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[7] with ethyl chloroformate in benzene–pyridine.

(*b*) A solution of **2** (0.1 g) and cyclohexylamine (0.1 g) in benzene (10 ml) was stored overnight at room temperature and then concentrated. Recrystallisation of the residue from ether–light petroleum gave 6-cyclohexylaminocarbonylamino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**6**), m.p. 130°, $[\alpha]_D^{30}$ −34°, ν_{max}^{Nujol} 3360 and 3280 (urea N–H), and 1630 cm^{-1} (urea C=O) (Found: N, 7.0. $C_{19}H_{32}N_2O_6$ calc.: N, 7.3%).

(*c*) Using essentially the procedure in (*b*) but with butylamine, 6-butylaminocarbonylamino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**7**) was obtained as a hygroscopic solid, m.p. 70°, $[\alpha]_D^{30}$ −37°, ν_{max}^{Nujol} 3440 and 3380 (urea N–H), and 1660 cm^{-1} (urea C=O) (Found: C, 56.3; H, 8.5; N, 7.5. $C_{17}H_{30}N_2O_6$ calc.: C, 56.9; H, 8.4; N, 7.8%).

(*d*) Using essentially the procedure in (*a*) but with propargyl alcohol and elution of the crude product from Kieselgel 7734 (Merck) with ether–light petroleum (1:1), 6-deoxy-1,2:3,4-di-*O*-isopropylidene-6-(2-propynyloxy)carbonylamino-α-D-galactopyranose (**4**, 94%) was obtained having b.p. 175°/0.07 mmHg, $[\alpha]_D^{30}$ −32°, ν_{max}^{liquid} 3450 and 3360 (carbamate N–H), 3300 (≡C–H), 2120 (C≡C), and 1740 cm^{-1} (carbamate C=O) (Found: C, 56.0; H, 6.8; N, 3.8. $C_{16}H_{23}NO_7$ calc.: C, 56.3; H, 6.8; N, 4.1%).

A solution of **4** (0.65 g) in ethanol (10 ml) was added to a suspension of Amberlite IR-120 (H^+) resin (10 ml) in water (10 ml), and the mixture was stirred at 70° and monitored by t.l.c. (Kieselgel 7731, methanol–ethyl acetate, 1:3). After 6 h, the mixture was filtered and concentrated. Recrystallisation of the residue (0.48 g) from ethanol–light petroleum gave 6-deoxy-6-(2-propynyloxy)carbonylamino-D-galactose (**8**, 0.26 g, 52%), m.p. 153–154°, $[\alpha]_D^{30}$ +60° (equil., water) (Found: C, 45.7; H, 5.8; N, 5.1. $C_{10}H_{15}NO_7$ calc.: C, 46.0; H, 5.8; N, 5.4%). N.m.r. data (methyl sulphoxide-d_6, internal acetonitrile $\delta = 2.00$): δ 7.20 (*m*, NH), 6.55 (*d*, *J* 7 Hz, HO-1β), 6.15 (*d*, *J* 5 Hz, HO-1α), 4.60 (*d*, *J* 2 Hz, C≡C–CH_2); α/β-ratio 2:1).

N,N′-*Di*-(*6-deoxy-1,2:3,4-di*-O-*isopropylidene-α-*D-*galactopyranos-6-yl*)*urea* (**5**). — A solution of the isocyanate **2** (1 g) and 1,1-diphenyl-2-propyn-1-ol (1.4 g) in benzene (25 ml) and triethylamine (1 ml) was boiled under reflux until the i.r. band at 2250 cm^{-1} (C=N) disappeared (4 days). Addition of light petroleum then gave **5** (0.4 g), m.p. 210–211°, $[\alpha]_D^{30}$ −50.5°, ν_{max}^{Nujol} 3350 and 3320 (urea N–H), and 1625 cm^{-1} (urea C=O) (Found: N, 5.0. $C_{25}H_{40}N_2O_{11}$ calc.: N, 5.2%). Mass spectrum: *m/e* 529 $(M-15)^+$. N.m.r. data (deuteriochloroform, internal tetramethylsilane): τ 4.5 (*d*, $J_{1,2}$ 6 Hz, 2 × H-1), 4.9 (*q*, NHCONH), 5.4 (*q*, $J_{2,3}$ 2.5, $J_{3,4}$ 7.0 Hz, 2 × H-3), 5.6–8.0 (2nd order, 2 × H-2, H-4, H-5, H-6 and H-6′), 8.5, 8.6, 8.7 (*s*, 8Me).

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