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Preliminary communication

The reaction of *O*-protected glycosides of 2-benzamido-2-deoxy-β-D-glucose with trimethylsilyl chloride–sodium hydride and subsequent reduction with lithium aluminium hydride*

ROY GIGG** and ROBERT CONANT

Laboratory of Lipid and General Chemistry, National Institute for Medical Research, Mill Hill, London NW7 1AA (Great Britain)

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Derivatives of 2-benzamido-2-deoxy-D-glucose can be converted[1] into derivatives of 2-benzylamino-2-deoxy-D-glucose by way of the 2-*N*-allylbenzamido derivatives. Reduction of the *N*-allylbenzamido derivatives with lithium aluminium hydride gave the *N*-allylbenzylamino derivatives in good yield and these were isomerised to *N*-(prop-1-enyl)benzylamino derivatives with potassium *tert*-butoxide in dimethyl sulphoxide. The *N*-(prop-1-enyl)benzylamino derivatives hydrolysed spontaneously in the air to give the benzylamino derivatives.

The benzylamino derivatives can be *N*-acylated and, since 2-*N*-benzylacetamido-2-deoxy-D-glucose derivatives may be useful for the synthesis of 1,2-*cis*-glycosides, we have sought a more direct route to the benzylamino derivatives, using a method which would also preserve *O*-allyl groups rather than convert them into *O*-(prop-1-enyl) groups as in the above method.

In contrast to the rapid and high-yielding reduction of tertiary amides with lithium aluminium hydride, the reduction of secondary amides is slow and capricious due mainly to complex formation with the reagent[2,3], and attempts to reduce our 2-benzamido-2-deoxy sugars directly with lithium aluminium hydride were disappointing. Borane appears to be a superior reagent for the reduction of amides[4], but it also reacts with the double bond of allyl ethers and reductively cleaves[5] the dioxane and dioxolane rings of ketals.

In view of the ease of reduction of the tertiary amide group in the *N*-allylbenzamido derivatives[1] with lithium aluminium hydride, we investigated the reduction of the tertiary amides formed from the benzamido derivatives by the action of trimethylsilyl chloride and sodium hydride in tetrahydrofuran. Simple secondary amides are considered[6] to give *N*-silyl derivatives on silylation.

Allyl 2-benzamido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside[7] (1) was treated with an excess of sodium hydride and trimethylsilyl chloride in tetrahydrofuran at 20° for 1 h, to form the *N*-trimethylsilylbenzamido derivative 2, and then an

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**To whom correspondence should be directed.

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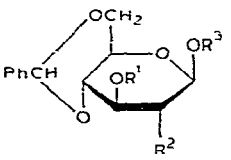
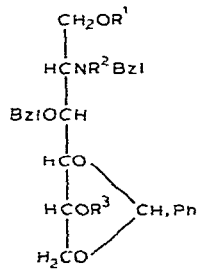
excess of lithium aluminium hydride was added. After 30 min at 20°, t.l.c. showed the formation of a new product. Ethyl acetate, methanol, and water were added and the crude product was chromatographed on silica gel, to give the benzylamino derivative **3** {30%, m.p. 94–95°, $[\alpha]_D^{25}$ −19° (*c* 1, chloroform)}. Isomerisation[8] of the allyl group in **3** with potassium *tert*-butoxide in dimethyl sulphoxide gave the known[1] prop-1-enyl glycoside **4**. With lithium aluminium hydride alone in tetrahydrofuran, no reaction of **1** was observed during 30 min at 20°.



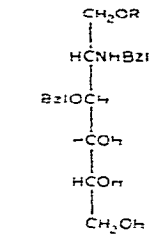
1 R^1 = Bzl, R^2 = NHBz, R^3 = $-CH_2CH{=}CH_2$
2 R^1 = Bzl, R^2 = N(Bz)$SiMe_3$, R^3 = $-CH_2CH{=}CH_2$
3 R^1 = Bzl, R^2 = NHBzl, R^3 = $-CH_2CH{=}CH_2$
4 R^1 = Bzl, R^2 = NHBzl, R^3 = $-CH{=}CHMe$
5 R^1 = R^3 = Bzl, R^2 = NHBz
6 R^1 = R^3 = Bzl, R^2 = NHBzl
7 R^1 = $-CH_2CH{=}CH_2$, R^2 = NHBz, R^3 = Bzl
8 R^1 = R^3 = $-CH_2CH{=}CH_2$, R^2 = NHBz



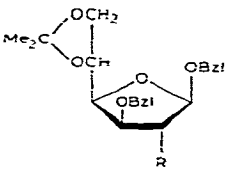
9 R^1 = Bzl, R^2 = R^3 = H
10 R^1 = Bzl, R^2 = R^3 = Ac
11 R^1 = Bzl, R^2 = Ac, R^3 = H
12 R^1 = R^3 = Bzl, R^2 = Ac
13 R^1 = $-CH_2CH{=}CH_2$, R^2 = R^3 = H
14 R^1 = $-CH{=}CHMe$, R^2 = R^3 = H

When benzyl 2-benzamido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside[9] (**5**) was treated as described for **1**, little reaction was observed, probably because of the very low solubility[9] of **5** in organic solvents. Therefore, the mixture of **5**, trimethylsilyl chloride, and sodium hydride was heated under reflux in tetrahydrofuran for 2 h and, after cooling, an excess of lithium aluminium hydride was added. After 30 min at 20°, t.l.c. showed the presence of only a small proportion of the anticipated benzylamino derivative[1] **6**. The major, more polar product {m.p. 111–112°, $[\alpha]_D^{25}$ −8° (*c* 1, chloroform)} was isolated (70% yield) by chromatography on silica gel, and characterized as 1,3-di-*O*-benzyl-2-benzylamino-4,6-*O*-benzylidene-2-deoxy-D-glucitol (**9**) as described below.

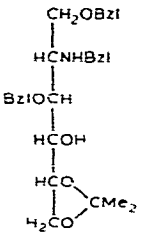
Compound **9** showed i.r. absorbtion for OH and/or NH, but not for amide, and acetylation gave a product (**10**) with ester and Amide I absorbtions in the i.r. spectrum. The immediate assumption, based on the analytical figures for **9**, was that the combination of reagents had reduced the benzamido group and reductively cleaved the benzylidene group, to give a monobenzylated diol as observed[10] in reactions with lithium aluminium hydride–aluminium chloride, but the *N*-acetylated, *O*-benzylated derivative **12** did not correspond with benzyl 3,4,6-tri-*O*-benzyl-2-*N*-benzylacetamido-2-deoxy-β-D-glucopyranoside prepared by benzylation of benzyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside[9]. Mild, acid hydrolysis of **9** (under conditions not expected to cleave a glycosidic linkage) gave a more polar product **15** {m.p. 68–70°, $[\alpha]_D^{26}$ +20° (*c* 1, chloroform)}. Hydrogenolysis of **9** in glacial acetic acid, over Pd/C during 12 h, gave



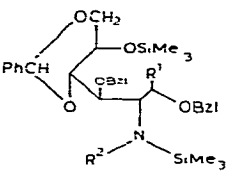
15 R = Bzl
16 R = $-CH_2CH{=}CH_2$
17 R = H



18 R = NHBz
19 R = NHBzl
20 R = $N(Bz)CH_2CH{=}CH_2$
21 R = $N(Bzl)CH_2CH{=}CH_2$
22 R = N(Bzl)CH=CHMe



23



24 R^1 = Cl, R^2 = Bz
25 R^1 = H, R^2 = Bzl

2-amino-2-deoxy-D-glucitol, characterised as the hydrochloride[11] {m.p. 164–166°, $[\alpha]_D^{25}$ −2° (*c* 1, water)} and the *N*-benzoyl derivative {m.p. 159–161°, $[\alpha]_D^{25}$ +5° (*c* 1, water); which was also prepared by reduction of 2-benzamido-2-deoxy-D-glucose[12] with borohydride}. Hydrogenolysis of the *N*-acetyl derivative **11**, prepared by alkaline hydrolysis of **10**, in glacial acetic acid over Pd/C for 3 days gave 2-acetamido-2-deoxy-D-glucitol[13] {m.p. 153–155°, $[\alpha]_D^{25}$ −11° (*c* 1, water)}.

Treatment of benzyl 3-*O*-benzyl-2-benzylamino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside[1] (**6**) with trimethylsilyl chloride–sodium hydride under reflux in tetrahydrofuran and subsequent treatment with lithium aluminium hydride also gave the glucitol derivative **9**. Similar treatment of benzyl 2-benzamido-3-*O*-benzyl-2-deoxy-5,6-*O*-isopropylidene-β-D-glucofuranoside[9] (**18**) with sodium hydride and trimethylsilyl chloride in tetrahydrofuran at 20°, or under reflux, gave mainly the 2-amino-2-deoxy-D-glucitol derivative **23** (a syrup which, on acid hydrolysis, also gave **15**) and only small proportions of the cyclic benzylamino derivative **19**. For comparison, **19** was prepared from **18** by way of the *N*-allylbenzamido derivative **20**, *N*-allylbenzylamino derivative **21**, and *N*-(prop-1-enyl)benzylamino derivative **22** by the general procedure described previously[1].

Silylation of **1** under reflux conditions and subsequent reduction with lithium aluminium hydride gave the glucitol derivative **13** (syrup, 75% yield), which was isomerised[8] to **14**. Acid hydrolysis of **13** gave the triol **16** {m.p. 72–73°, $[\alpha]_D^{26}$ +12.5° (*c* 1, chloroform)}, and acid hydrolysis of **14** gave the tetrol **17** {m.p. 128–130°, $[\alpha]_D^{25}$ +25° (*c* 1, methanol)}. Attempted removal of the prop-1-enyl group from **14** by mercuric chloride–mercuric oxide[13] gave a complex mixture, presumably due to oxazolidine formation between the mercuric chloride addition-compound of the prop-1-enyl group and the benzylamino group. A similar reaction was observed[13] (with formation of a mercurichloro derivative of a cyclic propylidene acetal) in attempts to remove a prop-1-enyl group with mercuric chloride–mercuric oxide when an adjacent free-hydroxyl group was present.

High-yielding, ring-opening reactions have also been observed when compounds **7**[1] and **8** {m.p. 267–270° (dec.), $[\alpha]_D^{26}$ −33° (*c* 0.3, *N*,*N*-dimethylformamide) prepared by the general procedure described previously[7]} were treated with trimethylsilyl chloride-sodium hydride at reflux in tetrahydrofuran and subsequent reduction with lithium aluminium hydride.

The mechanism of the formation of **9** from **5** possibly involves formation of the

chloro-ether **24** and subsequent reduction of the chloro-ether[14] and silylated benzamido group, to give **25**. Aqueous work-up then liberates the silyl groups to give **9**.

Preliminary observations on the reaction of glycosides of non-amino sugars under these conditions show that a reaction occurs more slowly than with the amino sugars, but the products have not been characterised.

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