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Note

Synthesis of derivatives of 4,6-diamino-4,6-dideoxy-D-gulose

YOUSIF ALI AND MEZHIR HUSSAIN
Department of Chemistry, University of Baghdad, A'damia, Baghdad (Iraq)
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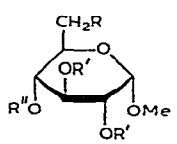
Amino sugars and their derivatives are of widespread occurrence in biologically active substances. A large number of diamino sugars have now been synthesised[1], but there are only a few examples in the *gulo* series either naturally occurring or synthetic. We now report the preparation of derivatives of 4,6-diamino-4,6-dideoxy-D-gulose.

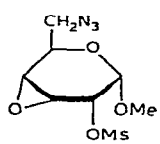
The conversion of the *gluco* into the *gulo* configuration can be effected[2] *via* a 3,4-anhydroalloside and *trans*-diaxial ring-opening.

The starting material, methyl 6-azido-4-*O*-benzoyl-6-deoxy-2,3-di-*O*-mesyl-α-D-glucopyranoside (**3**), was obtained from methyl 2,3,6-tri-*O*-mesyl-α-D-glucopyranoside[3] (**1**) by azide displacement to give **2**, followed by benzoylation. Alternatively, methyl 4,6-*O*-benzylidene-2,3-di-*O*-mesyl-α-D-glucopyranoside was treated[4] with *N*-bromosuccinimide followed by displacement of the 6-bromo substituent in the product **4** with azide to give **3**. Better yields of **3** were obtained by the second route.

Treatment[5] of **3** at room temperature with methanolic sodium methoxide effected debenzoylation and not anhydro-ring formation, and regenerated **2** in good yield. However, at reflux temperatures with a stoichiometric amount of methoxide, debenzoylation of **3** was complete within 30 min, and anhydro-ring formation proceeded slowly to give the epoxide **5**. The best yield of **5** was obtained after 8–10 h, although an appreciable amount of **2** was still present. Longer reaction times gave a complex mixture.



1 R = OMs, R' = Ms, R" = H
2 R = N_3, R' = Ms, R" = H
3 R = N_3, R' = Ms, R" = Bz
4 R = Br, R' = Ms, R" = Bz



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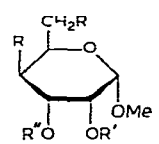

6 R = N_3, R' = Ms, R" = H
7 R = N_3, R' = R" = Ms
8 R = N_3, R' = R" = H
9 R = NH_2, R' = R" = H
10 R = NHBz, R' = R" = Bz
11 R = NH_2, R' = Ms, R" = H

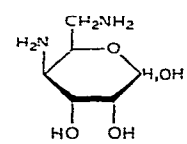

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TABLE I

P.M.R. DATA[a]

Parameter	*Compound*						
	2	**3**[b]	**4**[c]	**5**[d]	**7**	**8**[e]	**10**
H-1	4.97d	4.85d	4.86d	5.06o[f]	5.00cm	5.10d	4.87d
H-2	5.40q	5.28o[f]	5.28o[f]	4.92q		6.08t	4.59t
H-3	5.08q	4.61q	4.65t	6.45cm		5.85q	4.18q
H-4	6.20cm	4.73t	4.73t	5.775t	5.94q	6.24q	5.26cm
H-5		5.91cm	5.86cm	6.45cm	5.61cm	5.84cm	
H-6	6.43t	6.61d	6.53d		6.30q	6.38q	5.87o[f]
H-6′		6.62d	6.55d	6.60q	6.62q	6.73q	6.78o[f]
OCH_3	6.51s	6.46s	6.45d	6.54s	6.46s	6.50s	6.50s
OMs	6.82s, 6.862s	6.86s, 7.13s	6.86s, 7.12s	6.85s	6.75s, 6.88s	—	—
Bz	—	2.45cm	2.45cm	—	—	—	2.64cm, 2.14cm
OH	—	—	—	—	—	7.258b	—
NH	—	—	—	—	—	—	3.17d
$J_{1,2}$	3.5	3.5	3.5	5	3	3	3
$J_{2,3}$	9.8	10	10	2	—	3	3
$J_{3,4}$	8	9.3	9	4.5	2	1.5	2
$J_{4,5}$	—	9.3	9	4.5	4	3.5	—
$J_{6,5}$	—	5.5	3	—	3	3	7
$J_{6,5}$	—	3.8	7	—	4	4	5
$J_{6,6'}$	—	—	—	4.5	6.5	6.5	10

[a]Chemical shifts (τ values) and first-order coupling constants (Hz) for solutions in $CDCl_3$ at 100 MHz. Key: s, singlet; d, doublet; t, triplet; q, quartet; cm, complex multiplet; o, octet; b, broad. [b]$J_{2,5}$ 0.9, [c]$J_{2,5}$ 1.2, [d]$J_{1,3}$ 1, $J_{1,4}$ 0.9 Hz. [e]In $CDCl_3$ + 1 drop of C_5D_5N. [f]Assignment verified by spin decoupling.

Treatment of **5** with sodium azide in aqueous ethanol, in the presence of ammonium chloride at reflux temperatures for 5 h, afforded a syrupy mixture containing a major and two minor products which showed strong i.r. absorptions for azide and hydroxyl. Treatment of the mixture with mesyl chloride gave a crystalline dimesylate **7**, the p.m.r. spectrum of which was consistent with a product formed by a *trans*-diaxial opening of the epoxide group in **5**. The signals for H-6 and H-6′ have similar chemical shifts when the 4-substituent of the pyranoid ring is equatorial, but not when it is axial[6]. Our assignments agreed with these observations (Table I). Thus, **7** is methyl 4,6-diazido-4,6-dideoxy-2,3-di-*O*-mesyl-α-D-guloside, and the major product of the ring-opening of **5** must be methyl 4,6-diazido-4,6-dideoxy-2-*O*-mesyl-α-D-gulopyranoside (**6**). Similar results have been reported[7] for the ring-opening of methyl 3,4-anhydro-6-deoxy-α-D-allopyranoside with sodium acetate, which gave methyl 4-*O*-acetyl-6-deoxy-α-D-gulopyranoside as the major product.

Treatment of **6** with a stoichiometric amount of sodium ethoxide, at reflux temperature in ethanol for 5 h, afforded methyl 4,6-diazido-4,6-dideoxy-α-D-gulopyranoside (**8**), which consumed 1.1 mol of periodate, indicating the presence of vicinal hydroxyl groups. Reduction of **8** with hydrazine hydrate–Raney nickel in

methanol at reflux temperature gave methyl 4,6-diamino-4,6-dideoxy-α-D-gulopyranoside (**9**), which was characterised as the tetrabenzoyl derivative **10**.

Reduction of the 4,6-diazido-2-mesylate derivative **6** with hydrazine–Raney nickel gave the crystalline 4,6-diamino-2-mesylate **11** in good yield.

Attempts to obtain the diamino sugar **12** by treatment of **9** with boiling 1, 2, or 5% hydrochloric acid gave a complex mixture.

EXPERIMENTAL

Melting points were determined electrothermally and are uncorrected. P.m.r. spectra (internal Me_4Si) were recorded with a Varian A-100 spectrometer for solutions in chloroform-*d*, acetone-d_6, or pyridine-d_5. Optical rotations were determined with a Perkin–Elmer 141 polarimeter (1-cm cell). T.l.c. was performed on silica gel (Merck, type 60), with detection by charring with sulphuric acid. Silica gel GF 254 (Merck) was also used and detection effected with u.v. light. Concentration was performed under reduced pressure at 40° (bath). Column chromatography was performed on Whatman Chromedia silica gel SG 31 and SG 33.

*Methyl 6-azido-6-deoxy-2,3-di-*O*-mesyl-α-*D*-glucopyranoside* (**2**). — A mixture of methyl 2,3,6-tri-*O*-mesyl-α-D-glucopyranoside[4] (**1**, 0.4 g) and sodium azide (0.4 g) in *N,N*-dimethylformamide (10 ml) was heated at ~100° for 2 h. The cooled mixture was poured into water and extracted with chloroform (3 × 20 ml). The combined extracts were washed with water, dried ($MgSO_4$), and concentrated. Crystallisation of the syrupy residue gave **2** (0.13 g, 37.1%), and recrystallization from ethanol gave material having m.p. 101–103°, $[\alpha]_D$ +96° (*c* 0.5, chloroform) (Found: C, 29.20; H, 4.72; N, 10.91; S, 17.44. $C_9H_{17}N_3O_9S_2$ calc.: C, 28.80; H, 4.53; N, 11.20; S, 17.07%).

*Methyl 6-azido-4-*O*-benzoyl-6-deoxy-2,3-di-*O*-mesyl-α-*D*-glucopyranoside* (**3**). — (*a*) Conventional treatment of **2** with benzoyl chloride–pyridine and elution of the crude product from silica gel with chloroform–methanol (3:1) gave **3**, m.p. 130–132° (from methanol), $[\alpha]_D$ +58° (*c* 0.62, chloroform); lit.[5] m.p. 130–132° $[\alpha]_D$ +59.2°. *(b)* A solution of methyl 4-*O*-benzoyl-6-bromo-6-deoxy-2,3-di-*O*-mesyl-α-D-glucopyranoside (**4**; 6 g, 12 mmol) and sodium azide (6 g) in *N,N*-dimethylformamide (60 ml) was stirred at ~100° for 2 h and then diluted with water. The precipitate was collected, washed with water, and dried to give the crude product (5.5 g). Recrystallization from methanol gave **3** as bright plates, m.p. 130–132°, $[\alpha]_D$ +57° (*c* 0.53, chloroform).

*Methyl 3,4-anhydro-6-azido-6-deoxy-2-*O*-mesyl-α-*D*-allopyranoside* (**5**). — Compound **3** (2 g) was added to methanolic sodium methoxide (prepared from 0.1 g of sodium and 40 ml of methanol), and the mixture was boiled under reflux for 10 h. T.l.c. (chloroform–methanol, 16:1) revealed that debenzoylation was complete in 30 min, with slow conversion of **2** into **5**. The cooled mixture was diluted with water and extracted thrice with chloroform. The extract was washed with water, dried ($MgSO_4$), and concentrated, and the brown syrup was crystallised from ether to

give the crude product (0.58 g, 50%). Decolorisation and recrystallisation from methanol gave white needles of **5**, m.p. 96–97°, $[\alpha]_D$ +64° (*c* 0.57, chloroform) (Found: C, 34.32; H, 4.95; N, 14.88; S, 11.65. $C_8H_{13}N_3O_6S$ calc.: C, 34.40; H, 4.65; N, 15.05; S, 11.46%).

*Methyl 4,6-diazido-4,6-dideoxy-2,3-di-*O*-mesyl-α-*D*-gulopyranoside* (**7**). — A suspension of **5** (0.6 g) in ethanol (18 ml) was treated with a solution of sodium azide (0.6 g) and ammonium chloride (0.6 g) in water (6 ml). The resulting mixture was boiled under reflux and stirred for 5 h, and then cooled, diluted with water, and extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and concentrated to give **6** as a colourless syrup (0.69 g).

The foregoing compound (0.69 g) was mesylated in pyridine in the usual way, and the crude product (0.8 g, 94.1%) was recrystallised twice from ethanol to give **7**, m.p. 123–123.5°, $[\alpha]_D$ +44° (*c* 0.9, chloroform) (Found: C, 27.22; H, 4.08; N, 20.75; S, 16.08. $C_9H_{16}N_6O_8S_2$ calc.: C, 27.00; H, 4.00; N, 21.00; S, 16.00).

*Methyl 4,6-diazido-4,6-dideoxy-α-*D*-gulopyranoside* (**8**). — A solution of ethanolic sodium ethoxide (from 0.2 g of sodium and 24 ml of ethanol) was added to a solution of crude **6** (1.4 g) in ethanol (10 ml), and the mixture was boiled under reflux for 5 h. T.l.c. (chloroform) then showed a single product with mobility less than that of **8**. The mixture was diluted with water and extracted with chloroform. The extract was dried and concentrated, and the syrupy residue was decolorized to give a pale-yellow syrup. Elution of the product from silica gel with chloroform gave **8** (0.7 g, 66.7%), $[\alpha]_D$ +71° (*c* 1, chloroform) (Found: C, 34.70; H, 5.31. $C_7H_{12}N_6O_4$ calc.: C, 34.43; H, 4.92%).

To a solution of **8** (62 mg) in 20% aqueous methanol (25 ml) was added 0.01M potassium periodate (75 ml). The mixture was kept in the dark, and the consumption of oxidant was monitored by the arsenite method. After 2 h, 1.1 mol of oxidant had been consumed.

*Methyl 4,6-diamino-4,6-dideoxy-2-*O*-mesyl-α-*D*-gulopyranoside* (**11**). — To a solution of **6** (0.69 g) in methanol were added hydrazine hydrate (25 ml) and Raney nickel (3 ml). The mixture was boiled under reflux for 1.5 h, cooled, filtered, and concentrated. The colourless, syrupy residue was crystallised from hot ethanol to give **11** (0.45 g, 77.7%) as the dihydrate, m.p. 203° (dec.), (Found: C, 31.30; H, 6.49; N, 9.08. $C_8H_{18}N_2O_6S \cdot 2H_2O$ calc.: C, 31.37; H, 7.18; N, 9.15).

*Methyl 4,6-dibenzamido-2,3-di-*O*-benzoyl-4,6-dideoxy-α-*D*-gulopyranoside* (**10**). — To a solution of syrupy **8** (0.28 g) in methanol (5 ml) were added hydrazine hydrate (7 ml) and Raney nickel (1 ml), and the mixture was boiled under reflux for 1.5 h. The cooled mixture was filtered through Hyflo Super-cell and then concentrated to give the syrupy diamino derivative **9** (0.2 g, 90.9%). Crystallisation from ethanol gave very hygroscopic, white crystals, $[\alpha]_D$ +103° (*c* 0.85, water), which were treated with dry pyridine (20 ml) and benzoyl chloride (4 ml) in the usual manner. Crystallisation of the crude product (0.2 g, 31.7%) from methanol gave **10**, m.p. 313°

(dec.), $[\alpha]_D$ +45° (*c* 0.9, chloroform) (Found: C, 69.68; H, 5.27; N, 4.46. $C_{35}H_{32}N_2O_8$ calc.: C, 69.08; H, 5.26; N, 4.61).

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