BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 51 (12), 3661—3662 (1978)

Reactions of Benzyl 2-Benzyloxycarbonylamino-2-deoxy-3-*O*-mesyl-α-D-gluco- and -α-D-allopyranoside Derivative with Iodide

Hiroshi SANO, Seiji IIMURA, Tsutomu TSUCHIYA,* and Sumio UMEZAWA
Institute of Bioorganic Chemistry, 1614 Ida, Nakahara-ku, Kawasaki 211

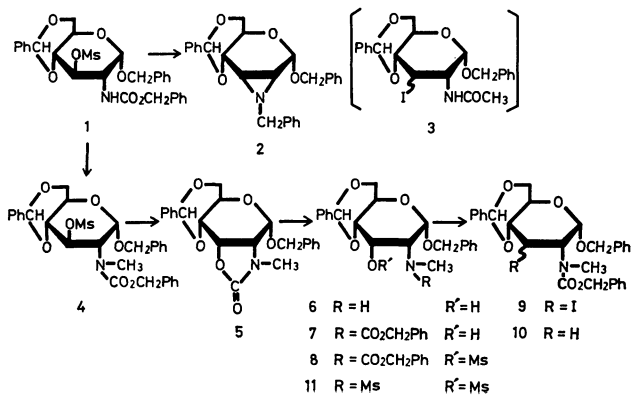
(Received June 5, 1978)

Synopsis. The reactions of benzyl 4,6-*O*-benzylidene-2-benzyloxycarbonylamino-2-deoxy-3-*O*-mesyl-α-D-glucopyranoside (**1**), its *N*-methyl derivative (**4**) and 3-epimer (**8**) with sodium iodide in DMF were studied. Compound **1** gave several products including 2,3-alloepimine, **4** an oxazolidinone and **8** a 3-iodo derivative.

A number of synthetic C-3′ and C-3″ deoxy derivatives of aminoglycoside antibiotics were found to be active against resistant bacteria.[1-3] As reported,[4] 3-iodination of a kanamycin B derivative having 2,6-dideoxy-2,6-bis(ethoxycarbonylamino)-3-*O*-tosyl-α-D-glucopyranosyl moiety was successfully performed in the synthesis of tobramysin in spite of the presence of syn-diaxial interaction[5] between axial anomeric oxygen and a nucleophile approaching axially to C-3. We are interested in a similar iodination of sulfonyloxy derivatives of related aminosugars. We have studied the displacement reaction at C-3 of benzyl 4,6-*O*-benzylidene-2-benzyloxycarbonylamino-2-deoxy-3-*O*-mesyl-α-D-glucopyranoside[6] (**1**) and related compounds with iodide ion.

Treatment of **1** with 50% (W/V) sodium iodide in *N*,*N*-dimethylformamide (DMF) at 100 °C for 48 h gave three products. The major product (14% yield) was not the corresponding 3-iodo derivative but *N*-benzyl-2,3-epimino-α-D-allopyranoside (**2**). Its structure was evidenced by identity with the compound prepared by benzylation of benzyl 4,6-*O*-benzylidene-2,3-epimino-α-D-allopyranoside. Since the starting material was recovered by a similar treatment of **1** without sodium iodide, it is apparent that iodide ion plays an important role in this reaction though the mechanism of this reaction remains equivocal. One of the other two minor products was found to be an iodo derivative (2-amino-3-iodo derivative) on the basis of IR and NMR spectra and microanalysis of its acetylated product (**3**).

In order to examine the effect of *N*-methyl group on the above reaction, the *N*-methyl derivative (**4**) was prepared by methylation of **1** and treated with sodium iodide in DMF in a similar manner to that described for **1**. In this case, an oxazolidinone (**5**) was the sole product isolated (71% yield), identical with the specimen obtained by alkaline treatment[7] of **4**.



In order to examine the configurational effect at C-3, 3-epimer of **4**, *i.e.* 3-*O*-mesyl-α-D-allopyranoside derivative (**8**) was prepared from **5**. Basic hydrolysis of **5** gave the allo-aminol (**6**), which was *N*-benzyloxycarbonylated to give **7**. Mesylation of **7** gave **8**. Treatment of **8** with sodium iodide in DMF afforded the 3-iodo derivative (**9**) in 33% yield. Its structure was characterized by reduction with Raney nickel, giving 3-deoxy compound (**10**).

Since the direct iodination at C-3 is more or less restricted by syn-diaxial interaction in both reactions of epimeric 3-mesylates (**4** and **8**), it is suggested that the neighboring 2-*N*-benzyloxycarbonyl group plays an important role in the reaction of iodide ion,[8] participating in the elimination of the mesyloxy group. For the sake of confirmation, we have prepared a 2-*N*-mesyl derivative (**11**), which is assumed to take no such participation. By treatment of **11** with sodium iodide the starting material was mainly recovered along with some minor products containing no iodine.

Experimental

*Reaction of **1** with Sodium Iodide in DMF.* Dry sodium iodide (3.0 g) was added to a solution of **1** (300 mg) in dry DMF (4.5 ml) and the mixture was heated at 100 °C for 48 h. The chloroform extracts of the reaction mixture were concentrated by addition of toluene. The solution of the residue in chloroform was washed with 5% sodium thiosulfate solution and water, dried (Na_2SO_4), and concentrated. The thick syrup (287 mg) was chromatographed with silica gel (Wakogel C-200) with benzene–ethyl acetate (30: 1→1: 1, gradual change). From the earlier fractions, a solid (74 mg; TLC, R_f 0.75 with benzene–ethyl acetate 9: 1) was obtained, which was further purified by chromatography with hexane–benzene (1: 5→1: 10). Recrystallization from ethanol gave needles of **2**, 32 mg (14%), mp 165—166 °C, $[\alpha]_D^{25}$ + 120° (*c* 0.2, chloroform). Found: C, 75.53; H, 6.70; N, 2.98%. Calcd for $C_{27}H_{47}NO_4$: C, 75.50; H, 6.34; N, 3.26%.

1 (27 mg, R_f 0.5) was recovered from the middle fractions described above; a solid (24 mg; TLC, R_f 0.13) from the latest fractions. Acetylation of the solid gave a solid (13 mg) [IR (KBr): 1740, 1700, 1650, 1540 cm^{-1}] and another solid (**3**, 14 mg), IR (KBr): 1660, 1560 cm^{-1}; PMR (pyridine-d_5): δ 2.15 (3H s, Ac). Found: C, 52.18; H, 4.85; N, 2.76; I, 24.42%. Calcd for $C_{22}H_{24}NO_5I$: C, 51.88; H, 4.75; N, 2.75; I, 24.91%.

*Benzyl N-Benzyl-4,6-O-benzylidene-2,3-dideoxy-2,3-epimino-α-D-allopyranoside (**2**).* Sodium (10.3 mg) dissolved in 2-propanol (0.45 ml) was added to a solution of **1** (103 mg) in dry dioxane (1.4 ml), and the mixture was treated in a similar

way to that reported by Rhoads and Gross.[9] To a solution of the crude epimine (51 mg) in DMF (1.0 ml) were added benzyl bromide (0.06 ml) and silver oxide (70 mg) and the mixture was stirred at room temperature for 14 h. Usual purification gave a solid. Recrystallization from ethanol gave needles, 49 mg (32%), mp 165—166 °C, $[\alpha]_D^{25}+120°$ (*c* 0.2, chloroform). PMR ($CDCl_3$): 2H unresolved q centered at δ 2.18 (H-2,3) (J=6 Hz), which sharpened on irradiation at δ 5.05. Found: C, 75.24; H, 6.51; N, 2.97%. Calcd for $C_{27}H_{27}NO_4$: C, 75.50; H, 6.34; N, 3.26%.

Benzyl 4,6-O-Benzylidene-2-benzyloxycarbonylamino-2-deoxy-3-O-mesyl-2-N-methyl-α-D-glucopyranoside (4). Methyl iodide (0.22 ml) and silver oxide (408 mg) were added to a solution of **1** (503 mg) in dry DMF (10 ml) and the mixture was stirred vigorously at room temperature for 15 h. Work-up in the usual manner gave a solid. Recrystallization from ethyl acetate–hexane gave rods (496 mg, 97%), mp 160—162 °C, $[\alpha]_D^{21}+67°$ (*c* 2, chloroform). IR (KBr): 1690 cm^{-1} (amide I); the peak at 1540 cm^{-1} (amide II) was not observed. PMR ($CDCl_3$): δ 2.91 and 3.12 (each 3H s, SO_2CH_3 and NCH_3). Found: C, 61.88; H, 5.80; N, 2.46; S, 5.21%. Calcd for $C_{30}H_{33}NO_9S$: C, 61.74; H, 5.70; N, 2.40; S, 5.49%.

Benzyl 4,6-O-Benzylidene-2-N:3-O-carbonyl-2-deoxy-2-methylamino-α-D-allopyranoside (5). By Use of Sodium Iodide in DMF: Dry sodium iodide (0.83 g) was added to a solution of **4** (83 mg) in dry DMF (1.2 ml) and the mixture was heated at 100 °C for 48 h. Work-up in the usual manner gave a solid. Recrystallization from ethyl acetate gave rods, 40 mg (71%), mp 229—230 °C, $[\alpha]_D^{21}+190°$ (*c* 2, chloroform). IR (KBr): 1775 cm^{-1} (cyclic carbamate). PMR ($CDCl_3$): δ 2.82 (3H s, NCH_3), 5.06 (1H d, J=5 Hz, H-1), 5.64 (1H s, C_6H_5CH=). Found C, 66.69; H, 5.98; N, 3.54%. Calcd for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52%.

By Use of Sodium Acetate: Sodium acetate trihydrate (431 mg) was added to a solution of **4** (431 mg) in 2-methoxyethanol (8.6 ml), and the mixture was refluxed for 45 h. Work-up in the usual manner gave a solid. Recrystallization from ethyl acetate gave rods, 256 mg (85%), mp 229—230 °C.

Benzyl 4,6-O-Benzylidene-2-deoxy-2-methylamino-α-D-allopyranoside (6). A solution of **5** (232 mg) in ethanolic 0.5 M potassium hydroxide (6.9 ml) was refluxed for 24 h. Work-up in the usual manner gave a solid. Recrystallization from ethyl acetate gave needles, 181 mg (85%), mp 210—211 °C, $[\alpha]_D^{31}+99°$ (*c* 1, chloroform). PMR ($CDCl_3$): δ 2.28 (1H m, H-2) which collapsed to a triplet (J=3.5 Hz) on deuteration; 2.48 (3H s, NCH_3), 5.08 (1H d, J=3.5 Hz, H-1). Found: C, 67.80; H, 6.80; N, 3.71%. Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77%.

Benzyl 4,6-O-Benzylidene-2-N-benzyloxycarbonyl-2-deoxy-2-methylamino-α-D-allopyranoside (7). Work-up in the usual manner gave a thick syrup (86%), $[\alpha]_D^{26}+79°$ (*c* 2, chloroform). PMR ($CDCl_3$): δ 3.32 (3H s, NCH_3). Found: C, 68.90; H, 6.22; N, 2.73%. Calcd for $C_{29}H_{31}NO_7$: C, 68.91; H, 6.18; N, 2.77%.

Benzyl 4,6-O-Benzylidene-2-N-benzyloxycarbonyl-2-deoxy-3-O-mesyl-2-methylamino-α-D-allopyranoside (8) was prepared from **7** in the usual manner; a thick syrup (97%), $[\alpha]_D^{30}+88°$ (*c* 2, chloroform). PMR ($CDCl_3$): δ 2.97 (3H s, SO_2CH_3), 3.32 (3H s, NCH_3), 5.07 (1H d, J=3.5 Hz, H-1), 5.45 (1H t, J=2.5 Hz, H-3). Found: C, 61.90; H, 5.80; N, 2.47; S, 5.41%. Calcd for $C_{30}H_{33}NO_9S$: C, 61.73; H, 5.70; N, 2.40; S, 5.49%.

Benzyl 4,6-O-Benzylidene-2-N-benzyloxycarbonyl-2-deoxy-3-iodo-2-methylamino-α-D-gluco or allopyranoside (9). Dry sodium iodide (1.32 g) was added to a solution of **8** (132 mg) in dry DMF (2.6 ml) and the mixture was heated at 100 °C for 48 h. The solution contained at least 6 components (TLC, R_f 0, 0.1, 0.4, 0.45 (weak, **8**), 0.55 and 0.6 (major, **9**), with benzene–ethyl acetate=15:1). Separation of the products in a similar manner to that for the reaction of **1** with NaI gave a thick syrup of **9**, which crystallized on standing; 46 mg (33%). Recrystallization from benzene–hexane gave needles, mp 180—183 °C, $[\alpha]_D^{29}+28°$ (*c* 2, chloroform). PMR ($CDCl_3$): δ 3.02 and 3.04 (each s, 3H in total, NCH_3). Found: C, 56.55; H, 4.83; N, 2.20; I, 20.25%. Calcd for $C_{29}H_{30}NO_6I$: C, 56.59; H, 4.91; N, 2.28; I, 20.62%.

Benzyl 4,6-O-Benzylidene-2-N-benzyloxycarbonyl-2,3-dideoxy-2-methylamino-α-D-ribohexopyranoside (10). Hydrogenation of **9** (11.4 mg) in dioxane (0.2 ml) with Raney nickel (0.2 ml) and triethylamine (trace) gave a syrup, 5.6 mg (62%), $[\alpha]_D^{25}+132°$ (*c* 1, chloroform); PMR ($CDCl_3$): δ 1.8—2.5 (2H m, H-3, 3′), 3.01 (3H s, NCH_3). Found: C, 71.40; H, 6.49; N, 2.96%. Calcd for $C_{29}H_{31}NO_6$: C, 71.14; H, 6.38; N, 2.86%.

Benzyl 4,6-O-Benzylidene-2-deoxy-3-O-mesyl-2-methylsulfonylamino-2-N-methyl-α-D-allopyranoside (11). Hydrogenation of **8** (40 mg) in dioxane (1.5 ml) with palladium black gave a syrup (29 mg, 96%); PMR ($CDCl_3$): δ 2.49 (3H s, NCH_3), 2.29 (3H s, SO_2CH_3). Mesylation of the syrup in the usual manner gave a syrup, 17 mg (97%), $[\alpha]_D^{24}+58°$ (*c* 1, chloroform); PMR ($CDCl_3$): δ 2.87 and 2.93 (each 3H s, NSO_2CH_3 and NCH_3), 3.25 (3H s, SO_2CH_3). Found: C, 52.85; H, 5.65; N, 2.45%. Calcd for $C_{23}H_{29}NO_9S_2$: C, 52.36; H, 5.54; N, 2.65%.

References

1) S. Umezawa, *Adv. Carbohydr. Chem. Biochem.*, **30**, 111—182 (1974); H. Umezawa, *ibid.*, **30**, 183—225 (1974).

2) H. Sano, T. Tsuchiya, S. Kobayashi, M. Hamada, S. Umezawa, and H. Umezawa, *J. Antibiot.*, **29**, 978 (1976).

3) D. Ikeda, F. Nagaki, S. Umezawa, T. Tsuchiya, and H. Umezawa, *J. Antibiot.*, **28**, 616 (1975).

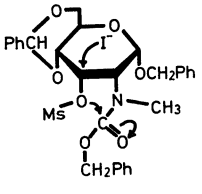
4) Y. Takagi, T. Miyake, T. Tsuchiya, S. Umezawa, and H. Umezawa, *J. Antibiot.*, **26**, 403 (1973); *Bull. Chem. Soc. Jpn.*, **49**, 3649 (1976).

5) A. C. Richardson, *Carbohydr. Res.*, **10**, 395 (1969).

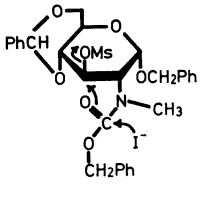
6) P. H. Gross and H. K. Zimmerman, Jr., *Liebigs Ann. Chem.*, **674**, 211 (1964).

7) For example see: L. Goodman, *Adv. Carbohydr. Chem.*, **22**, 109—175 (1967).

8) For the cooperation of iodide ion and the neighboring group, we assume the following mechanisms (I) and (II) for the reactions of **8** and **4**, respectively. Though in the reaction of **8**, there is syn-diaxial interaction between the leaving mesyloxy anion and the axial anomeric oxygen in the transition state, iodination can be facilitated by the presence of the benzyloxycarbonyl group as depicted in I.



I



II

9) W. D. Rhoads and P. H. Gross, *Carbohydr. Res.*, **11**, 561 (1969).