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Preliminary communication

A new method for *N*-demethylation of 2-deoxy-2-methylamino-α-D-glucopyranoside derivatives by air oxidation using palladium in aqueous 1,4-dioxane

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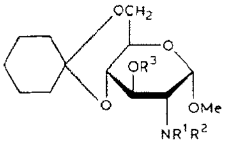
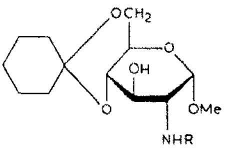
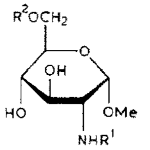
During research on derivatization of dihydrostreptomycin, we found that hydrogenation of methyl 2-*N*-benzyloxycarbonyl-4,6-*O*-cyclohexylidene-2-deoxy-2-methylamino-3-*O*-methylsulfonyl-α-D-glucopyranoside (**1**) with palladium black in aqueous 1,4-dioxane gave traces of a substance having lower t.l.c. mobility than the expected and principal de(*N*-benzyloxycarbonyl)ated product (**2**). This minor compound was identified as the corresponding *N*-demethyl derivative (**3**), $[\alpha]_D^{25}$ +89° (chloroform) from the following characteristics: *m/z* 351 (M^+); ^{1}H-n.m.r. ($CDCl_3$): δ 2.72 (dd, 1 H, $J_{1,2}$ 3.5, $J_{2,3}$ 9 Hz, H-2), 3.13 (s, 3 H, SO_2CH_3), 3.39 (s, 3 H, OCH_3), 4.60 (t, $J_{3,4}$ 9 Hz, H-3), and 4.81 (d, 1 H, H-1), and the fact that **3** was the same as the product of catalytic hydrogenation of methyl 2-benzyloxycarbonylamino-4,6-*O*-cyclohexylidene-2-deoxy-3-*O*-methylsulfonyl-α-D-glucopyranoside (**4**). The latter was prepared from the corresponding 3-hydroxy precursor[1] (**5**) by methylsulfonylation. The yield of **3** from **1** was greatly enhanced (10–35%) if air was bubbled into the mixture. This finding suggests that, after de(*N*-benzyloxycarbonyl)ation of **1**, oxidative *N*-demethylation may occur.



	R^1	R^2	R^3
1	Me	CO_2CH_2Ph	Ms
2	Me	H	Ms
3	H	H	Ms
4	H	CO_2CH_2Ph	Ms
5	H	CO_2CH_2Ph	H
6	H	CO_2Me	H



7 R = Me
8 R = H



9 R^1 = Me, R^2 = H
10 R^1 = R^2 = H
11 R^1 = Me, R^2 = $SiMe_2(CMe_3)$
12 R^1 = H, R^2 = $SiMe_2(CMe_3)$

Birkenmeyer and Dolak[2] described a similar *N*-dealkylation in lincomycin and its analogues; an aqueous solution of lincomycin was treated with oxygen (or air) in the pre-

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sence of platinum catalyst to give the 1′-*N*-demethyllincomycin in moderate yield. Davis and Rosenblatt[3] described oxidation of an *N*-methyl group in a tertiary amine into *N*-formyl on treatment with oxygen and platinum catalyst. More recently, Nagabhushan *et al.*[4] prepared *N*-demethylgentamicins by treating gentamicins with iodine and sodium acetate in aqueous methanol. Photochemical *N*-demethylation of sisomicin by utilizing the *N*-2,4-dinitrophenyl derivative has also been reported[4]. However, the yields of these *N*-demethylated products were moderate or low. In the field of alkaloids, *N*-dealkylation of tertiary amines has been performed by using phenyl chloroformate[5] or vinyl chloroformate[6].

The foregoing evidence and our experimental results prompted study of the *N*-demethylation reaction with a more fundamental example, methyl 4,6-*O*-cyclohexylidene-2-deoxy-2-methylamino-α-D-glucopyranoside (**7**), $[\alpha]_D^{25}$ +91° (H_2O) [^{1}H-n.m.r. (C_6D_5N): δ 2.61 (s, 3 H, NCH_3), 2.94 (dd, $J_{1,2}$ 3, $J_{2,3}$ 9 Hz, H-2), and 3.45 (s, 3 H, OCH_3)], which was prepared from the *N*-methoxycarbonyl precursor[7] **6** with lithium aluminum hydride. Trial experiments revealed some characteristics of this reaction, which were (*a*) the *N*-demethyl derivative **8** [methyl 2-amino-4,6-*O*-cyclohexylidene-2-deoxy-α-D-glucopyranoside[1], $[\alpha]_D^{25}$ +113° (chloroform); lit.[1] +113° (chloroform)] began to be formed only after pre-bubbling of air (~1.5 h); (*b*) the mixture, initially slightly basic, became acidic (pH ~1) after long bubbling; and (*c*) the yield of **8** fluctuated (15–45%) in each experiment. Concerning (*b*), in order to maintain constant pH of the mixture, a borate buffer (pH 9) was added, and this afforded a dramatic increase and constancy in the yield (~90%) of **8**. Replacement of the borate buffer by 0.2M ammonium carbonate (pH 8.8) also proved successful. When the procedure [2:5 1,4-dioxane–0.2M ammonium carbonate, air bubbling for 10 h, and then 20 h after replacement with fresh catalyst] was applied to **7** {$[\alpha]_D^{25}$ +73° (chloroform); ^{1}H-n.m.r. (C_6D_5N): δ 3.26 (s, 6 H) and 3.32 (s, 3 H) (NCH_3, OCH_3, SO_2CH_3)}, the *N*-demethyl derivative **3** was obtained in 74% yield, together with a trace of **2**, [**2**, unstable; ^{1}H-n.m.r. (C_6D_5N): δ 2.45 (s, 3 H, NCH_3), 2.80 (dd, 1 H, $J_{1,2}$ 3.5, $J_{2,3}$ 10 Hz, H-2), 3.26 and 3.32 (each s, 3 H, OCH_3, SO_2CH_3), and 4.82 (t, 1 H, H-3)].

To evaluate the solvent effect on the reaction of **7**, 1,4-dioxane was replaced by oxolane, but this led to a slight decrease in the yield of **8**. When the aqueous buffer (borate or ammonium carbonate) was used without addition of 1,4-dioxane, no reaction occurred and the starting compound (**7**) was recovered quantitatively. As 1,4-dioxane and other ether-type solvents are known to give unstable peroxides[8] on exposure to air, a peroxide may participate in the reaction. This assumption was partly substantiated by the finding (*a*) already described. No reaction occurred, as expected, in the absence of palladium. These results indicate that both palladium and 1,4-dioxane (or other ether-type solvents) are essential in this reaction.

N-Demethylation of methyl 2-deoxy-2-methylamino-α-D-glucopyranoside[9] (**9**) did not proceed smoothly in 1,4-dioxane–buffer, and gave methyl 2-amino-2-deoxy-α-D-glucopyranoside (**10**) in only ~20% yield after 2 days of air bubbling (the catalyst was replaced once with fresh catalyst), and the starting **9** (~35%) was recovered. The difficulty of the reaction was attributed to the presence of the primary hydroxyl group at C-6, which could be oxidized to an aldehyde or other reactive group and poison the catalyst, and therefore the hydroxyl group was protected. Treatment of **9** with *tert*-butylchlorodimethylsilane gave the 6-*O*-silylated derivative (**11**), $[\alpha]_D^{25}$ +85° (chloroform); *m/z* 321 (M^+); ^{1}H-n.m.r. ($CDCl_3$–20% ND_3 in D_2O): δ 0.1 (s, 6 H, $SiMe_2$), 0.91 (s, 9 H, *tert*-butyl), 2.44 (dd, $J_{1,2}$ 3.5, $J_{2,3}$ 10 Hz, H-2), 2.45 (s, 3H, NCH_3), 3.39 (s, 3 H, OCH_3), and 4.83 (d, 1 H, H-1). The *N*-demethylation of **11** proceeded smoothly to give the desired product (**12**) in high yield, proving the foregoing assumption.

A typical procedure, as exemplified by **11**, is as follows. To a solution of **11** (72 mg) in 1,4-dioxane (10 mL) was added borate buffer (6 mL; pH 9; composed of 25 mM boric acid, 25 mM potassium chloride, and 21 mM sodium hydroxide) and freshly prepared palladium black (2 mL) was sedimented in the buffer, and air was bubbled in with stirring for 6 h at room temperature. Filtration followed by concentration of the filtrate gave a residue that was dissolved in chloroform and the solution was washed with water, dried (sodium sulfate), and evaporated to give **12** as a ninhydrin-positive amorphous powder; yield 65 mg (94%); $[\alpha]_D^{25}$ +80° (chloroform); *m/z* 307 (M^+); ^{1}H-n.m.r. ($CDCl_3$–20% ND_3 in D_2O): δ 0.1 (s, 6 H), 0.91 (s, 9 H), 2.65 (dd, $J_{1,2}$ 3.5, $J_{2,3}$ 10 Hz, H-2), 3.39 (s, 3 H, OCH_3) and 4.64 (d 1 H, H-1).

In summary, this new *N*-demethylation procedure is easy, and gives high yield of the product if the primary hydroxyl group is protected. Studies on the mechanism, and the scope and limitations of the reaction, are under way.

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