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ISOPROPYLIDENATION WITH 2,2-DIMETHOXYPROPANE–*N*,*N*-DIMETHYLFORMAMIDE–*p*-TOLUENESULFONIC ACID. SELECTIVE SUBSTITUTION IN CERTAIN AMINOCYCLITOLS

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ABSTRACT

The behavior of a variety of *N*-acetyl- and *N*-(benzyloxycarbonyl)-aminocyclitols with 2,2-dimethoxypropane–*N*,*N*-dimethylformamide–*p*-toluenesulfonic acid has been examined. Both *cis*- and *trans*-vicinal hydroxyl groups are readily bridged to give 1,3-dioxolanes. In one (sterically favorable) case, the reagent linked the nitrogen atom of an acetamido group with a vicinal hydroxyl group to give an *N*-acetyl-2,2-dimethyloxazolidine; this heterocyclic system is less labile to acid than are the 1,3-dioxolanes.

INTRODUCTION

Recent work in a number of laboratories[1–5] has amply demonstrated the fact that a mixture of 2,2-dimethoxypropane, *N*,*N*-dimethylformamide, and a trace of *p*-toluenesulfonic acid constitutes a unique acetonating agent capable, *inter alia*, of protecting vicinal, *trans*-diequatorial, hydroxyl groups[3] and of forming *N*-acetyl-2,2-dimethyloxazolidines from vicinal hydroxyl and acetamido groups[5]. The present paper describes some further explorations of the potential utility of this reagent for syntheses in the aminocyclitol field.

RESULTS AND DISCUSSION

Initially, we turned our attention to the *O*-isopropylidene derivative of *N*,*N'*-bis(benzyloxycarbonyl)-2-deoxystreptamine, the preparation of which through the action of the reagent on **1** had been described earlier[3]. At that time, the racemic structure corresponding to **2a**† had been assigned to this product, a decision which appeared to be amply justified when the compound was subsequently condensed with 3-acetamido-2,4,6-tri-*O*-benzyl-3-deoxy-α-D-glucopyranosyl chloride to give two

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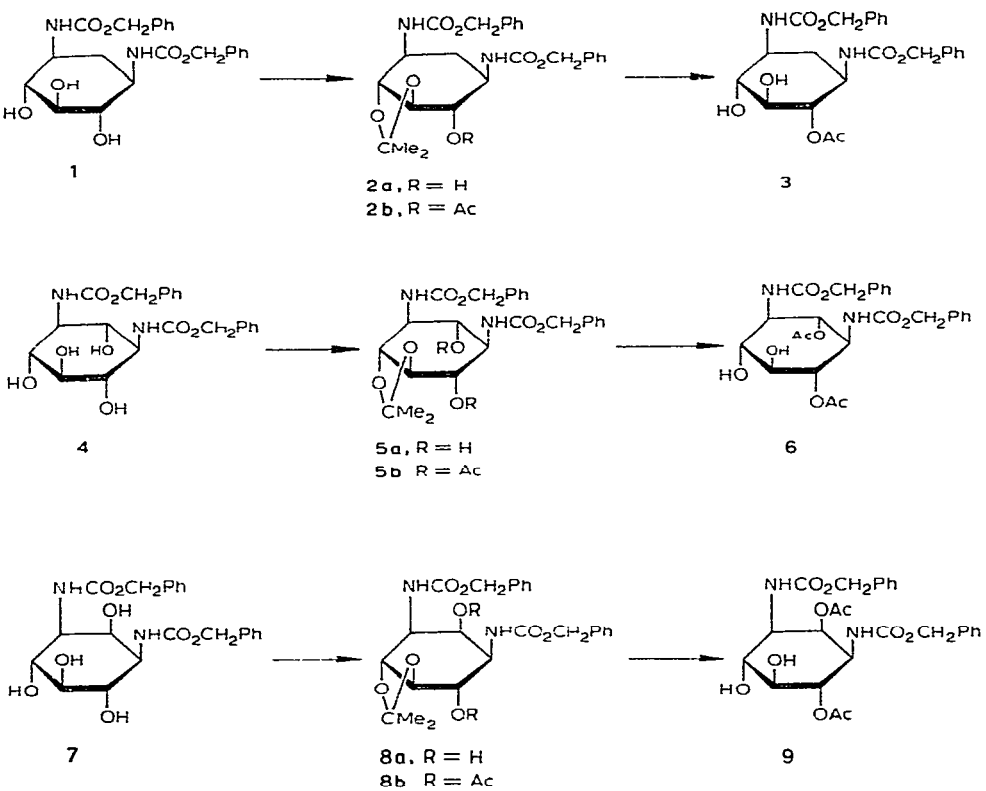
†Racemic structures are represented by only one formula.

diastereoisomeric α-D-hexopyranosides, one of which was found to be related to Kanamycin. We now present simple and independent evidence that structure **2a** is, indeed, the correct one. The compound yielded a crystalline acetate (**2b**) from which the highly acid-labile isopropylidene group could be cleaved under very mild conditions. The product, also crystalline, was found to reduce one mole-equivalent of periodate and, as acetyl migration under the conditions of the de-isopropylidenation is highly unlikely, we may regard formula **3** as depicting the final product, and **2a** and **2b** as representing its precursors. The isopropylidene derivative of *N,N'*-diacetyl-2-deoxystreptamine, reported earlier[3], presumably has a structure analogous to **2a**.

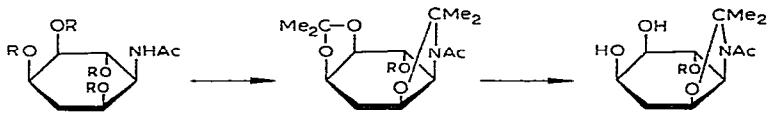
Treatment of *N,N'*-bis(benzyloxycarbonyl)streptamine[6] (**4**) with 2,2-dimethoxypropane–*p*-toluenesulfonic acid–*N,N*-dimethylformamide at 80° led to the isolation of a monoisopropylidene derivative in 76% yield. The i.r. absorption spectrum of the compound showed the nitrogen functions to be unaltered, and a crystalline di-*O*-acetyl derivative was readily obtained. Cleavage of the isopropylidene group from the latter afforded a product that consumed one mole-equivalent of periodate and, hence, is the racemate corresponding to **6**; this indicated that the acetonation product from **4** is **5a**.

A diastereoisomer of **4**, namely, 1,3-bis(benzyloxycarbonylamino)-1,3-dideoxy-*myo*-inositol[7] (**7**), gave, at room temperature, a crystalline monoisopropylidene



derivative in 57% yield. A crystalline diacetate therefrom was readily de-isopropylidenated, giving a periodate-labile di-*O*-acetyl-1,3-bis(benzyloxycarbonylamino)-1,3-dideoxy-*myo*-inositol which may be written as **9**; this showed that the isopropylidene group in its precursors is at the 5,6 (4,5) oxygen atoms (**8a** and **8b**).

10 11



12a, R = Ac
12b, R = H

13a, R = H
13b, R = Ac

14a, R = Ac
14b, R = H

Isopropylidenation of the racemate corresponding[8] to **10** with the mixture of reagents under investigation gave, in 81% yield, a crystalline isopropylidene derivative having an i.r. spectrum which showed that the acetamido group was unchanged. The same product could also be obtained by conventional acetonation with acetone and anhydrous copper(II) sulfate, and it is, therefore, concluded that the vicinal, *cis*-oxygen atoms had been bridged as depicted in formula **11**.

The deoxyinosamine **12b**, prepared by de-*O*-acetylation[9] of **12a**, was treated with 2,2-dimethoxypropane–*N*,*N*-dimethylformamide–*p*-toluenesulfonic acid at 80–90°, to yield an amorphous diisopropylidene derivative; the i.r. spectrum of this product clearly showed that the amide proton had been substituted. Acetylation gave a crystalline monoacetate that also had a trisubstituted nitrogen atom. The n.m.r. spectrum of this acetate showed, in addition to the *O*- and *N*-acetyl groups, two well-separated pairs of three-proton singlets, indicating the presence of two isopropylidene groups that differed in deshielding. Brief treatment with 50% aqueous acetic acid at 60–70° served to cleave one of the isopropylidene groups from the monoacetate, and gave a product which reduced one mole-equivalent of periodate and retained the trisubstituted nitrogen atom. It is apparent that acetonation of **12b** with the trio of reagents introduces an *N*,*O*-isopropylidene group, as well as an *O*,*O*-isopropylidene group, as shown by formula **13a**, and that the *O*,*O*-isopropylidene group is the more acid-labile of the two, permitting the deblocking process shown by **13b**→**14a**. Compound **14a** was further characterized through the removal of the *O*-acetyl group.

DISCUSSION

On the basis of these limited studies, it appears that vicinal, *trans*-diequatorial, hydroxyl groups are, indeed, readily isopropylidenated by this combination of reagents. There is no evidence that the nitrogen atom of a (benzyloxycarbonyl)amino

group and a vicinal hydroxyl group can be bridged, nor that an acetamido group can be linked to a vicinal *trans*-hydroxyl group. With a *cis* pair of hydroxyl groups and a hydroxyl group *cis* to an acetamido group, both *O,O*- and *N,O*-isopropylidene bridges can be established; the former of these is more labile to acid than the latter. Cleavage of *O,O*-isopropylidene groups can be achieved under conditions that do not appear to induce *trans*-*O,O*-acetyl migration.

EXPERIMENTAL

General. — Melting points are uncorrected. N.m.r. spectra were recorded with a Varian A-60 spectrometer. I.r. spectra were recorded with a Shimadzu AR-275 spectrophotometer. Column chromatography was performed with silicic acid (100 mesh; Mallinckrodt Chemical Works).

4(6)-O-Acetyl-N,N'-bis(benzyloxycarbonyl)-5,6(4,5)-O-isopropylidene-2-deoxystreptamine (**2b**). — Compound **2a** (ref. 3; 120 mg) was acetylated with pyridine–acetic anhydride overnight at room temperature, the mixture was poured into ice water, and the product was extracted with chloroform. The extract was washed with 10% sodium hydrogen carbonate solution and thrice with water, dried (anhydrous sodium sulfate), and evaporated *in vacuo*, to afford a crystalline residue After recrystallization from ether, the product was obtained as needles: wt. 125 mg (79%), m.p. 119°.

Anal. Calc. for $C_{27}H_{32}N_2O_8$: C, 63.20; H, 6 29; N, 5.47. Found: C, 63 06; H, 6.29; N, 5.58.

4(6)-O-Acetyl-N,N'-bis(benzyloxycarbonyl)-2-deoxystreptamine (**3**). — Compound **2b** (105 mg) was suspended in 50% aqueous acetic acid (10 ml), and the mixture was kept for 90 min at 70°; it was then evaporated *in vacuo*, to afford a crystalline product. Recrystallization from ethanol gave needles of **3** (85 mg, 88%), m.p. 175°; in aqueous solution at room temperature, the compound consumed 1.0 mole-equivalent of sodium metaperiodate.

Anal. Calc. for $C_{24}H_{28}N_2O_8$: C, 61.01; H, 5.97; N, 5.93. Found: C, 61.41; H, 5.86; N, 5.85.

N,N-Bis(benzyloxycarbonyl)-4,5(5,6)-O-isopropylidenestreptamine (**5a**). — A solution of **4** (ref. 6; 1.8 g) in dry *N,N*-dimethylformamide (20 ml) was heated at 80° and stirred while 2,2-dimethoxypropane (6 ml) and *p*-toluenesulfonic acid (100 mg) were added. The mixture was kept at 80°, the progress of the reaction being monitored by t.l.c.; after 2 h, the starting material was no longer detectable, and the acid present was removed by stirring the reaction mixture with Amberlite IRA-410 ion-exchange resin (~10 g) for 15 min. The suspension was filtered, and the filtrate was evaporated *in vacuo* at 40°; the residue was crystallized from ether–benzene, to give 1.5 g (76%) of **5a**. Recrystallization from ethanol afforded fine needles, m.p. 189°; i.r. data: ν_{max}^{Nujol} 3400 (OH), 3300 (NH), 1650, 1550 ($NHCO_2CH_2Ph$), and 840 cm^{-1} (isopropylidene).

Anal. Calc. for $C_{25}H_{30}N_2O_8$: C, 61.72; H, 6.22; N, 5.76. Found: C, 61.71; H, 6.28; N, 6.08.

2,4(2,6)-Di-O-acetyl-N,N'-bis(benzyloxycarbonyl)-5,6(4,5)-O-isopropylidene-

streptamine (**5b**). — Compound **5a** (200 mg) was acetylated with pyridine–acetic anhydride, overnight at room temperature, and the mixture was evaporated *in vacuo* (<40°) to give a crystalline solid. Recrystallization from methanol gave **5b**; wt. 210 mg (90%), m.p. 292°; i.r. data: ν_{max}^{Nujol} 3300 (NH), 1700, 1540 ($NHCO_2CH_2Ph$), 1740 (ester), and 850 cm^{-1} (isopropylidene).

Anal. Calc. for $C_{29}H_{34}N_2O_{10}$: C, 61.04; H, 6.01; N, 4.91. Found: C, 60.79; H, 6.31; N, 4.73.

2,4(2,6)-Di-O-acetyl-N,N'-bis(benzyloxycarbonyl)streptamine (**6**). — The cyclic acetal **5b** (100 mg) was dissolved in 50% aqueous acetic acid (20 ml), and the solution was kept for 90 min at 70°; t.l.c. then showed that the reaction was complete. The solution was evaporated *in vacuo*, to afford a crystalline solid which was recrystallized from ethanol to give **6** as colorless needles: wt. 80 mg (86%), m.p. 200°; i.r. data: ν_{max}^{Nujol} 3340 (NH), 1700, 1685, 1550, and 1535 ($NHCO_2CH_2Ph$), and 1740 cm^{-1} (ester). Dissolved in 0.05M sodium metaperiodate, **6** consumed 1.0 mole-equivalent of oxidant.

Anal. Calc. for $C_{26}H_{30}N_2O_{10}$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.70; H, 5.76; N, 5.42.

1,3-Bis(benzyloxycarbonylamino)-1,3-dideoxy-4,5(5,6)-O-isopropylidene-myo-inositol (**8a**). — To a stirred solution of the substituted inosadiamine **7** (ref. 7; 3.2 g) in dry *N,N*-dimethylformamide (30 ml) were added 2,2-dimethoxypropane (10 ml) and *p*-toluenesulfonic acid (100 mg). The mixture was stirred for 15 h at 25–27°; t.l.c. then failed to detect the presence of **7**. Amberlite IRA-410 ion-exchange resin was used to remove the acid, and the resulting solution was evaporated *in vacuo* to a syrup which was crystallized from ethanol. Compound **8a** was obtained as needles: wt. 2.0 g (57%), m.p. 125°.

Anal. Calc. for $C_{25}H_{30}N_2O_8$: C, 61.72; H, 6.22; N, 5.76. Found: C, 61.91; H, 6.34; N, 5.85.

2,4(2,6)-Di-O-acetyl-1,3-bis(benzyloxycarbonylamino)-1,3-dideoxy-5,6(4,5)-O-isopropylidene-myo-inositol (**8b**). — A solution of compound **8a** (300 mg) in a mixture of pyridine (2 ml) and acetic anhydride (1 ml) was kept overnight at room temperature, and then poured into ice–water. The product was extracted into chloroform and the extract was washed with 10% sodium carbonate solution and then thrice with water; moisture was removed with sodium sulfate, and the solution was evaporated *in vacuo*, giving a crystalline residue. On recrystallization from ethanol, compound **8b** was obtained in pure form: wt. 250 mg (71%), m.p. 206°.

Anal. Calc. for $C_{29}H_{34}N_2O_{10}$: C, 61.04; H, 6.01; N, 4.91. Found: C, 61.24; H, 6.22; N, 5.06.

2,4(2,6)-Di-O-acetyl-1,3-bis(benzyloxycarbonylamino)-1,3-dideoxy-myo-inositol (**9**). — The acetal **8b** (200 mg) was dissolved in 50% aqueous acetic acid (20 ml) and the solution was kept for 60 min at 70°; t.l.c. then showed that the reaction was complete. Evaporated *in vacuo*, the solution yielded a crystalline solid which was recrystallized from ethanol to give 160 mg (86%) of **9** as needles, m.p. 194–196°. The product consumed 1.0 mole-equivalent of sodium metaperiodate.

Anal. Calc. for $C_{26}H_{30}N_2O_{10}$: C, 58.86; H, 5.70; N, 5.28. Found: C, 59.03; H, 5.82; N, 5.37.

1DL-(3/1,2,4)-4-Acetamido-1,2-O-isopropylidene-1,2,3-cyclohexanetriol (**11**). — A solution of **10** (ref. 8; 200 mg) in *N,N*-dimethylformamide (10 ml) was heated at 80° and stirred while 2,2-dimethoxypropane (2 ml) and *p*-toluenesulfonic acid (10 mg) were added. The mixture was stirred for 2 h at 80°, cooled, and treated with Amberlite IRA-410 ion-exchange resin to remove the acid. The solution was then evaporated *in vacuo*, giving a solid which was recrystallized from ether to afford **11** as needles; wt. 195 mg (81%), m.p. 156°; i.r. data: ν_{max}^{Nujol} 3280 (OH), 3200 (NH), 1630 and 1540 (NHAc), and 870 cm^{-1} (isopropylidene). The same compound was obtained when **10** was treated with acetone in the presence of anhydrous copper(II) sulfate and a trace of sulfuric acid.

Anal. Calc. for $C_{11}H_{19}NO_4$: C, 57.62; H, 8 35; N, 6.11. Found: C, 57.90; H, 8.32; N, 6.00.

N-*Acetyl-3-deoxy-1,2*-N,O-*isopropylidene-5,6*-O-*isopropylidene*-epi-*inosamine-1* (**13a**). — Compound **12a** (ref. 9; 700 mg) was dissolved in 50 ml of methanol presaturated with ammonia, and the solution was kept overnight at room temperature. It was then evaporated *in vacuo* to give syrupy **12b**; this was dissolved in dry *N,N*-dimethylformamide (10 ml), and the solution was heated at 80° and stirred while 2,2-dimethoxypropane (2 ml) and *p*-toluenesulfonic acid (50 mg) were added. The mixture was heated for 2 h at 80–90°, the progress of the condensation being monitored by t.l.c. The mixture was then cooled, treated with Amberlite IRA-410 ion-exchange resin to remove the acid, and the solution evaporated *in vacuo* to a syrup which was chromatographed on a column of silicic acid (15 g) with 20:1 chloroform–methanol. The product (**13a**) was amorphous: wt. 350 mg (65%); i.r. data: ν_{max}^{Nujol} 3300 (OH), 1630 (NAc), and 860 cm^{-1} (isopropylidene).

Anal. Calc. for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.13; N, 4.91. Found: C, 58.80; H, 8.22; N, 4.78.

N-*Acetyl-6*-O-*acetyl-3-deoxy-1,2*-N,O-*isopropylidene-4,5*-O-*isopropylidene*-epi-*inosamine-1* (**13b**). — Compound **13a** (300 mg) was acetylated overnight at room temperature with a mixture of pyridine (5 ml) and acetic anhydride (2 ml). The mixture was then evaporated *in vacuo* to a syrup which was crystallized from ether–hexane; recrystallization from ether gave **13b** as needles: wt. 240 mg (70%), m.p. 143°; i.r. data: ν_{max}^{Nujol} 1730 (ester), 1650 (NAc), and 860 cm^{-1} (isopropylidene); n.m.r. signals ($CDCl_3$): τ 7.88 (6 H, NAc, OAc), 8.31 and 8.43 (*N,O*-isopropylidene), and 8.49 and 8.67 (*O,O*-isopropylidene).

Anal. Calc. for $C_{16}H_{25}NO_6$: C, 58.70; H, 7.70; N, 4 28. Found: C, 57.53; H, 7.68; N, 4.31.

N-*Acetyl-6*-O-*acetyl-3-deoxy-1,2*-N,O-*isopropylidene*-epi-*inosamine-1* (**14a**). — A solution of compound **13b** (500 mg) in 50% aqueous acetic acid (50 ml) was heated at 60–70°; after 60 min, the starting material was no longer detectable by t.l.c. The mixture was evaporated *in vacuo* to a syrup which was chromatographed on a column of silicic acid (15 g) with 20:1 chloroform–methanol. Compound **14a** was isolated as

an amorphous solid (350 mg, 89%) which consumed one mole-equivalent of sodium metaperiodate; i.r. data: ν_{max}^{Nujol} 3500–3300 (OH), 1740 (ester), 1630 (NAc), and 865 cm^{-1} (*N,O*-isopropylidene).

Anal. Calc. for $C_{13}H_{21}NO_6$: C, 54.34; H, 7.37; N, 4.88. Found: C, 54.39; H, 7.55; N, 4.59.

N-*Acetyl-3-deoxy-1,2*-N,O-*isopropylidene*-epi-*inosamine-1* (**14b**). — A solution of **14a** (35 mg) in ammonia-saturated methanol (10 ml) was kept overnight at room temperature. Evaporation *in vacuo* gave a solid which was recrystallized from ethanol to afford 25 mg (83%) of **14b**; m.p. 174–176°; i.r. data: ν_{max}^{KBr} 3500–3300 (OH), 1620 (NAc), and 850 cm^{-1} (*N,O*-isopropylidene). In aqueous solution at room temperature, the product consumed 1.0 mole-equivalent of sodium metaperiodate.

Anal. Calc. for $C_{11}H_{19}NO_5$: C, 53.86; H, 7 81; N, 5.71. Found: C, 53.68; H, 8.05; N, 5.45.

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