Communications to the Editors

THE SYNTHESIS OF 6-O-(3-AMINO-3-DEOXY-α-D-GLUCOPYRANOSYL)-2-DEOXYSTREPTAMINE

Sir:

In the previous papers[1,2], we have reported the total syntheses of paromamine and kanamycin C. We now wish to report the synthesis of 6-O-(3-amino-3-deoxy-α-D-glucopyranosyl)-2-deoxystreptamine[3,4] (3AD), which represents a portion of kanamycin A[5] and was first isolated by MAEDA *et al.*[3]

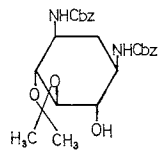
N,N'-Dicarbobenzoxy-2-deoxystreptamine, m.p. 236°C (decomp.), was treated with 2,2-dimethoxypropane and *p*-toluenesulfonic acid in N,N-dimethylformamide at 110°C for 4 hours to give a monoisopropylidene derivative (I) in racemic form in a quantitative yield, followed by recrystallization from ethyl acetate; the racemate: m.p. 145~146°C.

Found: C 63.63, H 6.69, N 5.85

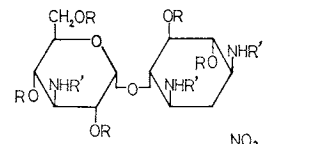
Calcd. for $C_{25}H_{30}N_2O_7$: C 63.82, H 6.43, N 5.95 %

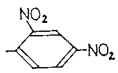
The condensation of I (racemic form) with 3-acetamido-2,4,6-tri-O-benzyl-3-deoxy-α-D-glucopyranosyl chloride* was conducted as follows: A sample (1.30 g) of I was dissolved in an anhydrous mixture (40 ml) of benzene-dioxane (4:1); Drierite (9 g), mercuric cyanide (0.91 g) and the glycosyl chloride (1.82 g) were added with stirring, and the mixture was then vigorously stirred at 100°C for 6 hours. The product was treated with 80 % acetic acid to remove the isopropylidene group, hydrogenated over palladium black in a mixture of dioxane - water - conc. hydrochloric acid (8:3:1) with occasional addition of water, and de-N-acetylated with 1 N barium hydroxide. The ninhydrin-positive product was dinitrophenylated with 2,4-dinitrofluorobenzene in aqueous ethanol in the presence of sodium bicarbonate and then O-acetylated with acetic anhydride and anhydrous sodium acetate. The resulting product, which showed about five spots with Rf-values of 0.3 (main), 0.37, 0.45, 0.51 and 0.56

Chart 1



I ; Cbz: $COOCH_2C_6H_5$





II: R = $COCH_3$; R' =

III: R, R' = H (3AD)

IV: R = H ; R' = $COCH_3$

on a silica-gel thin-layer chromatogram (TLC) with a solvent system (A): toluene-MEK (3:1), was chromatographed on a silica-gel column with the solvent mixture of benzene-MEK (4:1). The fractions having an Rf-value of about 0.3 were combined and then further separated into two fractions of nearly equal amount (Rf-values of 0.3 and 0.28) by preparative thin-layer chromatography using solvent system (A). The substance having an Rf-value of 0.30 was isolated and recrystallized from toluene-MEK affording yellow crystals of II; yield 340 mg (12 % over-yield from I); m. p. 195~198°C (decomp.), $[\alpha]_D^{18}$ +24° (c 0.9, acetone). IR spectrum (KBr disk): 3340, 3100, 1625, 1595, 1525, 1340, 745 (NH-DNP); 1760, 1370, 1225 (OAc) cm^{-1}.

Found: C 46.50, H 4.25, N 12.41

Calcd. for $C_{40}H_{41}N_9O_{24}$: C 46.56, H 4.01, N 12.22 %

On the other hand, the natural 3AD[3,4] was dini rophenylated and acetylated to give penta-O-acetyl-tri-N-(2,4-dinitrophenyl)-3AD; m.p. 194~198°C (decomp.), $[\alpha]_D^{18}$ +22° (c 1.0, acetone).

Found: C 46.44, H 4.21, N 12.36

Calcd. for $C_{40}H_{41}N_9O_{24}$: C 46.56, H 4.01, N 12.22 %

* This compound have been reported by S. UMEZAWA *et al.* in the abstracts of papers, 20 th Annual Meeting of the Chemical Society of Japan, Tokyo, Mar. 31, 1967, Vol. III, p. 596.

The melting point of II was not depressed by admixture with the above-mentioned derivative of natural 3AD. On TLC with a solvent system (A), the synthetic product II and the derivative of natural 3AD showed identical mobilities and their IR spectra were superimposable.

Hydrolysis of II with methanolic ammonia followed by treatment with an excess of Dowex 1X2 (OH^-) resin gave a crude free base, which was purified by chromatography on a column of Dowex 1X2 (OH^-) resin using water and recrystallized from aqueous methanol-ethanol to give a crystalline free base of III; $[\alpha]_D^{18}$ +98° (c 0.90, water).

Found : C 44.24, H 7.51, N 12.69
Calcd. for $C_{12}H_{25}N_3O_7$:
C 44.57, H 7.79, N 13.00 %

The natural 3AD base showed $[\alpha]_D^{18}$ +98° (c 0.10, water). On descending paper chromatography by ninhydrin coloration using a solvent system : *n*-butanol-pyridine-water-acetic acid (6 : 4 : 3 : 1), the R-value of the synthetic product III agreed with that of the natural 3AD. IR spectra of III and the natural 3AD were superimposable.

Finally, the absolute configuration of the synthetic product and its identity with the natural 3AD were confirmed by the copper complex method which has been reported from our Laboratory[6]. Tri-N-acetyl-3AD includes a pair of adjacent hydroxyl groups, which make a projected angle of about +60°, in the deoxystreptamine moiety, and showed $[\alpha]_{589}^{12}$ +80° (c 0.45, water), $\Delta[M]_{CuAm}$ +1590, as has been reported[4]. The free base III was N-acetylated with acetic anhydride in methanol to afford IV quantitatively; m. p. 236~239°C (decomp.), $[\alpha]_{589}^{18}$ +74° (c 0.91, water), $[\alpha]_{436}^{18}$ +140° (c 0.91, water), $[\alpha]_{436}^{18}$ +465° (c 0.80, CuAm), $\Delta[M]_{CuAm}$ + 1460. IR spectrum (KBr disk) : 3400, 1100~1000 (OH), 3290, 1650, 1560, 1375 (NH-Ac) cm^{-1}.

Found : C 47.91, H 6.99, N 9.08
Calcd. for $C_{18}H_{31}N_3O_{10}$:
C 48.10, H 6.95, N 9.35 %

If IV were a 4-O- or 5-O-linked derivative of 2-deoxystreptamine instead of the 6-O-linked derivative mentioned above, the $\Delta[M]_{CuAm}$ value would be about −1500 or nearly zero respectively. The observed value for $\Delta[M]$ of IV agreed with that of natural tri-N-acetyl-3AD within experimental error. Thus, the synthetic product III was proved to be identical with the natural 3AD. Since 2-deoxystreptamine has already been synthesized[7], the above synthesis is the first total synthesis of 6-O-(3-amino-3-deoxy-α-D-glucopyranosyl)-2-deoxystreptamine.

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