Communications to the editor

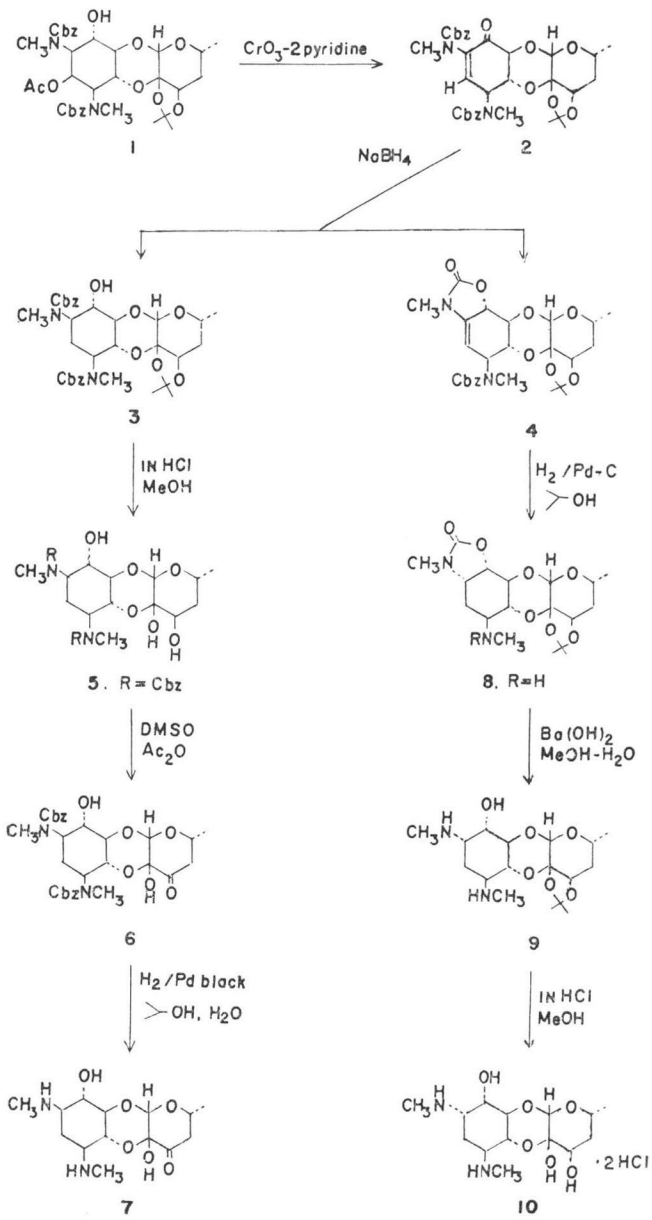
PREPARATION OF 7-DEOXYSPECTINOMYCIN AND 7-DEOXY-8-*EPI*-4(*R*)-DIHYDROSPECTINOMYCIN*

Sir:

A large number of aminocyclitol antibiotics contain 2-deoxystreptamine or its derivatives as the cyclitol unit. The cyclitol moiety *N,N'*-dimethyl-2-*epi*-streptamine appearing to be unique to spectinomycin. In the neamine[1] and sisomicin[2] antibiotics, an overall decrease in antibacterial activity was observed when the 2-deoxystreptamine unit was replaced by either streptamine or 2-*epi*-streptamine. Thus, it was of interest to prepare 7-deoxyspectinomycin** (**7**) in order to compare its activity with that of spectinomycin. In this paper we describe the preparation of 7-deoxyspectinomycin (**7**) and 7-deoxy-8-*epi*-4(*R*)-dihydrospectinomycin (**10**), as outlined in Scheme 1.

Many of the experimental methods employed in this work have been described in our earlier papers.[3,4] The route we employed for the preparation of 7-deoxy-*N,N'*-dicarbobenzoxy-spectinomycin (**6**) was similar to that recently reported*** except for the use of 7-*O*-acetyl-*N,N'*-dicarbobenzoxy-4(*R*)-dihydrospectinomycin-4,4a-acetonide (**1**)[6] as the starting material. Oxidation of **1** using the chromium trioxide-pyridine complex in methylene chloride afforded the unsaturated ketone **2** directly. Reduction of **2** using sodium borohydride in methanol yielded two major products, the desired 7-deoxy derivative **3** as reported[5], as well as a 49% yield

Scheme 1.



* Paper number IV in a series on Spectinomycin Chemistry.

** In the spectinomycin numbering system, the 7-position of spectinomycin corresponds to the 2-position of streptamine.

*** Following the completion of this work the preparation of **5** and **6** was reported by W. ROSENBROOK, *et al.*[5]

of the unsaturated cyclic carbamate **4**,* IR (KBr) 1788, 1698 cm^{-1}; Calcd. for $C_{26}H_{32}N_2O_9$: C 60.46, H 6.24, N 5.42; Found: C 60.38, H 6.23, N 5.41.

The triol **5**, obtained on acid hydrolysis of **3**, was oxidized using dimethylsulfoxide-acetic anhydride to yield the protected 7-deoxyspectinomycin **6**. Despite the earlier reported failure[5], hydrogenolysis of **6** (purified by preparative TLC using *n*-hexane - ethyl acetate - acetone, 5: 5: 3) using the palladium black-isopropanol-water conditions[3,4] proceeded without difficulty to afford crystalline 7-deoxyspectinomycin dihydrochloride (**7**), mp 195~199°C (dec), high resolution MS on the free base Calcd. for $C_{14}H_{24}N_2O_6$: (M^+) 316.1633; Found: (M^+) 316.1655.

The unsaturated cyclic carbamate **4** was subjected to catalytic hydrogenation-hydrogenolysis using 5% palladium on carbon to yield the 7-deoxy-8-*epi*-4(*R*)-dihydrospectinomycin cyclic carbamate **8**, PMR ($CDCl_3$) 4.42 (t, $J_{8,9}=7.0$ Hz, $J_{9,9a}=7.5$ Hz, *H*-9), 4.58 (s, *H*-10a). The 7 Hz coupling between *H*-8 and *H*-9 indicated a *cis* fused cyclic carbamate ring, since the couplings reported for a *trans* fused cyclic carbamate are 9~12 Hz.[7] The formation of a *cis* fused cyclic carbamate ring between C-8 and C-9 required that epimerization had occurred at one of these centers, and the 7.5 Hz coupling between *H*-9 and *H*-9a was only consistent with an equatorial hydroxyl group at C-9 (natural configuration). Hydrolysis of the cyclic carbamate ring in **8** (excess $Ba(OH)_2$ in refluxing methanol - water, 1: 1) gave the dihydrospectinomycin acetonide **9**, PMR (CD_3OD) 3.63 (t and dd, $J_{5a,9a}=J_{5a,6}=9.5$ Hz, *H*-5a; $J_{8,9}=4.5$ Hz, $J_{9,9a}=9.5$ Hz, *H*-9), 4.62 (s, *H*-10a), MS 358 (M^+). The observed coupling constants were in complete accord with the assignment of the *epi* configuration at C-8.** The acetonide protecting group in **9** was removed by acidic hydrolysis to afford crystalline 7-deoxy-8-*epi*-4(*R*)-dihydrospectinomycin dihydrochloride (**10**), mp 248°C (dec.); Calcd. for $C_{14}H_{26}N_2O_6 \cdot 2HCl$: C 42.97, H 7.21, N 7.16, Cl 18.12. Found: C 43.03, H 7.22, N 7.07, Cl 18.04.

* Using the reduction conditions reported in reference 5 the same two major products are obtained: **3** in 54% and **4** in 33% overall yield.

** For comparison, see the coupling constants reported in references 3 and 4.

The 7-deoxyspectinomycin (**7**) and 7-deoxy-8-*epi*-4(*R*)-dihydrospectinomycin (**10**) were found to be inactive when tested *in vitro* against 12 spectinomycin sensitive Gram-positive and Gram-negative organisms. Similarly, in agreement with the report of ROSENBROOK *et al.*[5] the 7-deoxy dihydrospectinomycin **5** (R=H) was found to be inactive when tested *in vitro*.

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