Table I

R^-M^+	Carbanion	Solvent	T, °C	% meso
n-BuLi	**2'**	THF	−78	>99
α-MeStLi[d]	**2'**	THF	−78	>99
n-BuLi	**2'**	THF	0	95
n-BuLi	**2'**	THF/Pyridine[b]	−78	83
α-MeStNa[d]	**2'**	THF	−78	96
α-MeSt(NaCE)[a,d]	**2'**	THF	−78	58
α-MeStK[d]	**2'**	THF	−78	65
α-MeStRb[d]	**2'**	THF	−78	57
$^-DD^-$, $2Li^+$[e]	**2''**	THF	−78	~50[c]

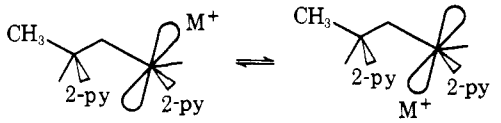
[a] 18-Crown-6 present in 10% excess. [b] 50% by volume. [c] Diastereomers not identified by NMR. [d] Prepared by reacting α-methylstyrene with the metal mirror in THF in vacuo (see ref 3). [e] $Li^+{}^-(Ph)_2C-(CH_2)_2-C(Ph)_2{}^-Li^+$, prepared by reacting 1,1-diphenylethylene with Li metal in THF, in vacuo.

quantities of the meso and racemic compound. Also, coordination of cation with strongly complexing molecules decreases the stereoselectivity. For instance, 18-crown-6 complexed Na salt is nonselectively methylated.[4]

The methylation stereochemistry of the Li salt of the corresponding 4-pyridyl derivative (**3''**) is also of interest. The methylation was not stereoselective in this case.

Epimerization studies on *meso*-**3'** in Me_2SO using *t*-BuOK as a catalyst indicate *meso*-**3'** and *rac*-**3'** to be of approximately equal stability, a result similar to that obtained by Flory and co-workers for the corresponding diphenylpentane.[5] Kinetic control of the reaction seems thus likely, a conclusion that is also supported by the very large differences in stereochemistry using different cations and coordinating agents.

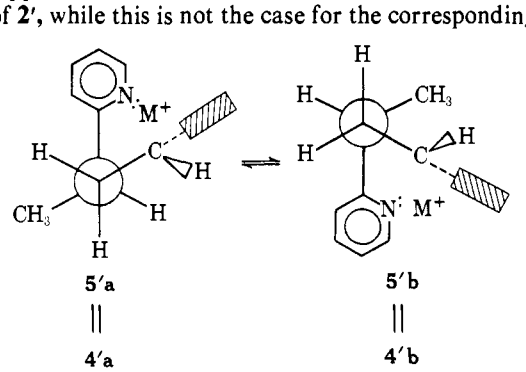
It is likely, on the basis of experimental results[6] and calculations[7] carried out on contact ion pairs[8] of these type of systems, that the counterion is present above (or below) the carbanion plane. Hence, two diastereomeric ion pairs should exist in principle, each of which may exist in several conformations. Barring greatly different reactivities of **4'a** and **4'b**



4'a **4'b**

the high methylation stereoselectivity of the Li (and Na) salt is consistent with the presence of either **4'a** or **4'b** and with either retention or inversion during methylation. Several recent reports on stereoselective alkylations of Li compounds indicate retention as the predominant mode of reaction.[1a-d] A cation side approach of electrophile seems reasonable, since anti approach would lead to an incipient product separated ion pair[9] in the transition state.[10]

It appears then that diastereomer **4'a** is favored for the Li salt of **2'**, while this is not the case for the corresponding salt of **2''**. This is unusual and seems only possible if other than steric factors are involved. Cation complexation with penultimate 2-pyridine has been demonstrated[11,12] for an almost identical Na carbanion salt and is likely to exist here also. Schematic representations of such cation complexed conformations are shown below. Inspection of models leads one to expect that **5'a** may be more stable than **5'b** because of nonbonded CH_3-pyridine lone pair interactions and because of an additional unfavorable gauche interaction in **5'b**. The proposed mechanism is also consistent with the observation that the stereoselectivity decreases with increasing cation size and cation coordination. It is further supported by the lack of stereoselectivity of the methylation of **2''**, where intramolecular pyridine–cation coordination is not possible.



5'a **5'b**

4'a **4'b**

Acknowledgment. This work was supported by the National Science Foundation under Grant DMR72-03130.

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C. F. Tien, T. E. Hogen-Esch*
Department of Chemistry, University of Florida
Gainesville, Florida 32611
Received April 12, 1976

A Chiral Synthesis of D-(+)-2,6-Dideoxystreptamine and Its Microbial Incorporation into Novel Antibiotics

Sir:

It has recently been shown[1-5] that suitable aminocyclitols can be converted microbiologically into antibiotics by mutants which lack the pathway for deoxystreptamine biosynthesis, but which when grown on a medium containing deoxystreptamine will form the appropriate antibiotic. For example a mutant of *S. fradiae* grown on a medium supplemented with deoxystreptamine biosynthesized neomycin. Analogues of deoxystreptamine such as streptamine and epistreptamine were also incorporated to give novel antibiotics.[1,2] This opens a route for

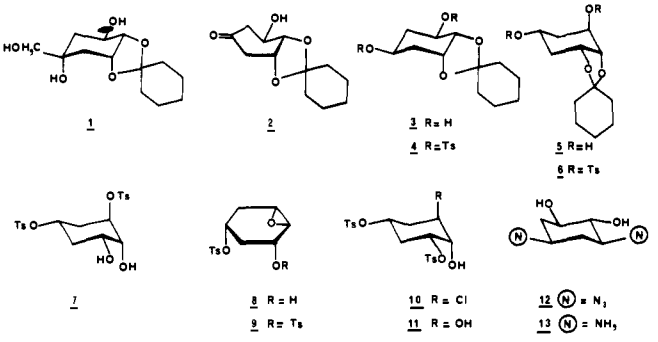
the production of new antibiotics specifically modified in the cyclitol ring, provided that suitable diaminocyclitol substrates are available. Such modified antibiotics may have less toxicity or increased activity against resistant strains of bacteria than the parent compounds.

In view of the importance of antibiotics substituted at position 4 or positions 4 and 5, and the desirability for microbial incorporation that modification to the deoxystreptamine structure should be as small as possible, it seemed attractive to prepare a chiral 2,6-dideoxystreptamine which if incorporated would give antibiotics in which the new deoxy group would appear at position 6 of the antibiotic. Since this work was completed a report of a derivative of a DL form of this compound has appeared.[6]

The *meso*-2-deoxystreptamine, although easily obtained by hydrolysis of natural antibiotics, is unsuitable for chiral synthesis. D-(−)-Quinic acid was therefore chosen as starting material and converted[7] into 3,4-*O*-cyclohexylidene-D-quinicol (**1**). Sodium metaperiodate oxidation of the triol (**1**) in aqueous solution at pH 5–6 gave crystalline 3L-3,4-*O*-cyclohexylidene 3,4/5-trihydroxycyclohexanone (**2**), mp 98 °C, $[\alpha]^{25}D$ +103° (*c* 1.36, $CHCl_3$) in quantitative yield. Lithium borohydride reduction in dimethoxyethane led to a 1:1 mixture in 90% yield of 1L-1,2,-*O*-cyclohexylidene 1,2/3,5-cyclohexanetetrol (**3**), mp 119–120 °C, $[\alpha]^{25}D$ −71.5° (*c* 2.4, CH_3Cl), separated from its epimer **5**, 1L-1,2-*O*-cyclohexylidene-1,2,5/3-cyclohexanetetrol, mp 130°, $[\alpha]^{25}D$ +6° (*c* 1.31, CH_3OH), by fractional crystallization. The absolute configuration of the monocyclohexylidene tetrols was established by hydrolysis to the known cyclohexanetetrols.[8,9] They were also converted into the corresponding ditosylates **4**, mp 114 °C, $[\alpha]^{25}D$ −48° (*c* 1.95, $CHCl_3$), and **6**, mp 105 °C, $[\alpha]^{25}D$ +22° (*c* 2.32, $CHCl_3$).

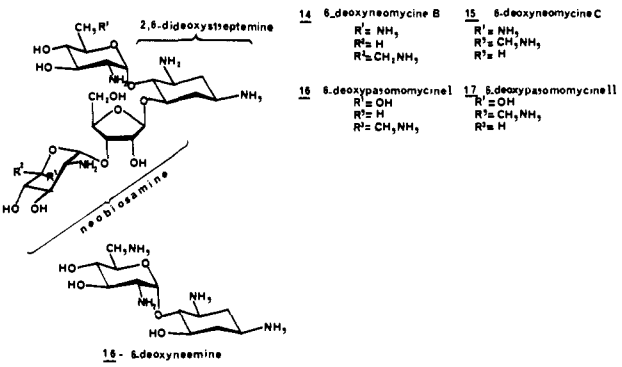
The synthesis of D-(+)-2,6-dideoxystreptamine was effected from ditosylate (**6**). Refluxing in 70% aqueous acetic acid gave the ditosyltetrol (**7**) which on treatment with methanolic sodium methoxide at room temperature was converted into the epoxide **8**, mp 120.5°, $[\alpha]^{25}D$ +40° (*c* 1.66, $CHCl_3$). Tosylation by *p*-toluene-sulfonyl chloride in pyridine at 20 °C for 18 h gave the ditosyl epoxide **9** mp 145 °C, $[\alpha]^{25}D$ +34° (*c* 1.93, $CHCl_3$) together with 1D-1/2,3,5-1-chloro-2-hydroxy-3,5-ditosyloxycyclohexane (**10**), mp 166 °C, $[\alpha]^{25}D$ +12° (*c* 1.74, $CHCl_3$), formed by chloride ion cleavage of the epoxide, which was quantitatively reconverted to the epoxide **9** by methanolic sodium methoxide.

The epoxide ring was opened by hydrolysis with 1 N aqueous sulfuric acid in dimethoxyethanol under reflux for 2.5 h to give exclusively the ditosyltetrol (**11**), mp 123 °C $[\alpha]^{25}D$ +10° (*c* 1.0, CH_3OH), in 90% yield and this in turn gave 1*D*-1,3,5/2-1,5-diazido-2,3-cyclohexanediol (**12**), mp 63.5 °C, $[\alpha]^{25}D$ +2° (*c* 1.0, CH_3OH), by azidolysis in refluxing dimethylformamide for 2 h, in 92% yield.



The diazide was reduced by Raney nickel to give the required 1*D*-1,3,5/2-1,5-diamino-2,3-cyclohexanediol (**13**), 1*D*-2,6-dideoxystreptamine in 94% yield, isolated as the crystalline dihydrochloride, mp 232 °C, $[\alpha]^{25}D$ +3.5° (*c* 1.17, H_2O), which has the same absolute configuration as the substituted deoxystreptamine of the natural antibiotics.

Using the methods of Rinehart and his co-workers[1,2] and the D⁻ mutants of *S. fradiae* (ATCC 2140) and S. rimosus forma *paromomycinus* (ATCC 21484), 2,6-dideoxystreptamine (**13**) was converted into the 6-deoxyneomycins and 6-deoxyparomomycins, respectively. These in turn were separated into their components 6-deoxyneomycins B (**14**) and C (**15**) and 6-deoxyparomomycins I (**16**) and II (**17**).



A 10% inoculum of D⁻ *S. fradiae* was added to a culture medium[2] supplemented with 25 mg/100 ml of 2,6-dideoxystreptamine, and the cultures were incubated at 28 °C with shaking for 5 days. The antibiotics and unchanged dideoxystreptamine were absorbed on an Amberlite IRC 50 cation exchange resin from which they were eluted with 2 N ammonium hydroxide. The eluate was concentrated and applied to a Sephadex G 10 column giving the 6-deoxyneomycins (22%) in the first fractions followed by 2,6-dideoxystreptamine. The compounds can also be separated by paper chromatography using 4:1 methanol:ammonium hydroxide solution as solvent and sodium hypochlorate/starch iodide[10] for detection. The R_f's were 0.26 and 0.62, respectively. Further paper-chromatographic separation of the 6-deoxyneomycins gave the components 6-deoxyneomycin B (**14**), R_f 0.29 and 6-deoxyneomycin C (**15**), R_f 0.21. Neomycins B and C had R_f's 0.25 and 0.165, respectively.

Confirmation of the structures was given by methanolysis to 6-deoxyneamine (**18**) and the methylneobiosaminides. The latter were chromatographically identical with the compounds obtained by methanolysis of neomycin. The structure of the 6-deoxyneamine was shown by N-acetylation and hydrolysis to give 2,6-diaminodideoxyglucose (neosamine C) and 2,6-dideoxystreptamine, and also by mass spectrometric comparison of the pertrimethylsilyl derivative with that of neamine. The mass spectra were very similar except that two peaks in neamine (*m/e* 343, 460) were shifted by 88 mass units in 6-deoxyneamine (*m/e* 25, 372) corresponding to substitution of $O\text{-}Si(CH_3)_3$ by H.

The microbiological spectra of the 6-deoxyneomycins were very similar to those of the neomycins, but 6-deoxyneomycin C was more potent against *E. coli*, *Proteus mirabilis*, *Staphylococcus aureus*, and *Salmonella typhimurium* than neomycin C whereas 6-deoxyneomycin B was less potent than neomycin B against these organisms.

6-Deoxyparomomycins I (**16**) and II (**17**) were formed when a similar medium was inoculated with D⁻ *S. rimosus* forma *paromomycinus*. The antibiotics were separated and the structures established by similar methods to those described for the deoxyneomycins. They had only about 25% of the antimicrobial activity of the corresponding paromomycins.

The ease of incorporation of 2,6-dideoxystreptamine into antibiotics by the two mutant organisms tested suggests that this aminocyclitol will prove to be of general use for the pro-

duction of a new range of deoxyaminocyclitol antibiotics.

All the substances described here have been characterized either by elemental analysis or physicochemical methods, especially proton and ^{13}C magnetic resonance.

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Jeanine Cleophax, Stephan D. Gero,* Jean Leboul
Institut de Chimie des Substances Naturelles, CNRS
91190 Gif sur Yvette, France

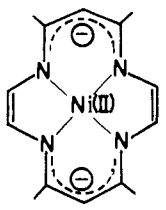
Muhammad Akhtar, John E. G. Barnett, Cedric J. Pearce
Department of Physiology and Biochemistry
Medical and Biological Sciences Building
Bassett Crescent East, Southampton SO9 3TU, England

Received June 30, 1976

Electrochemical Generation of a Dimeric Macrocyclic Complex

Sir:

The redox properties of synthetic macrocyclic complexes have attracted considerable interest.[1-4] It has been suggested that certain metal complexes containing antiaromatic tetraazamacrocyclic ligands ($4n\pi$) can be oxidized to the corresponding tetraazaanaluene compounds ($4n + 2$, π).[4] Although the aromatic structures have not yet been isolated and characterized, a number of physical techniques, primarily ESR, have shown that in the case of **1** (16π) the first oxidation process yields the π cation radial complex $[Ni^{II}L\cdot]^+$ (15π).[4,5] This complex actually exists in a dimer-monomer equilibrium with the dimer containing a Ni-Ni bond.[6] The compound also exhibits a second oxidation which presumably leads to the formation of the aromatic structure $[Ni^{II}L]^{2+}$ (14π). In the process of exploring the electrochemistry of some manganese(III) complexes containing the antiaromatic structure



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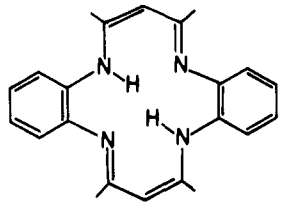
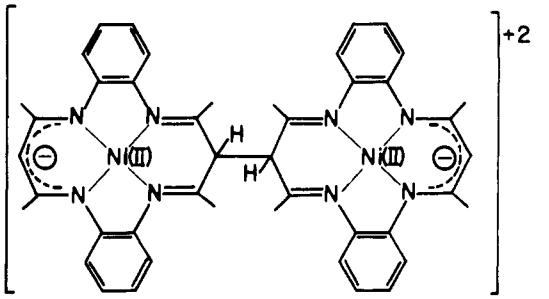


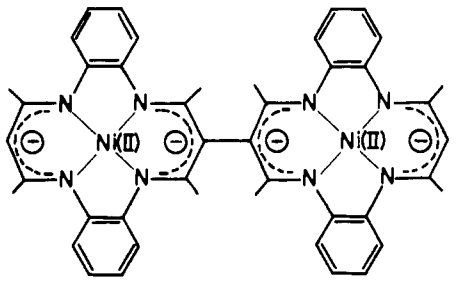
2

(24π), H_2[14]12eneN$_4$, **2**,[7,8] we investigated the oxidation behavior of Ni^{II}[14]12eneN$_4$. Electrochemical oxidation of Ni^{II}[14]12eneN$_4$ results in the formation of a dimeric compound composed of two macrocyclic units joined via a carbon-carbon single bond bridge, **3**.



3

The dimer is sensitive to bases and can be readily deprotonated to give **4**. Thus, in this case, the net effect of the electrochemical oxidation has been the joining of two macrocyclic structures via a radical mechanism to give a hindered biphenyl type macrocyclic dimer, **4**. Although both **1** and the nickel complex of **2** initially sustain a ligand oxidation, the distorted saddle shape of the later[9] apparently leads to the localization of the radical and ultimately radical dimerization via the organic framework. Thus, the attainment of the aromatic structure (in this case 22π) for this type of square planar macrocyclic complex appears to have a hitherto unrecognized structural dependency. This report treats the synthesis and characterization of **3** and **4** as well as the unusual conformational behavior of the protonated dimer, **3**, in solution.



4

Constant potential electrolysis of Ni^{II}[14]12eneN$_4$ in acetonitrile solution containing either 0.1 N Et_4NBF_4, $(n\text{-}Bu)_4NPF_6$, or $(n\text{-}Bu)_4NSO_3CF_3$ as a supporting electrolyte at 0.65 V[10] yielded the dark green moisture sensitive cation, **3**.[11] A plot of equivalent conductance Λ_e vs. $c^{1/2}$ for **3** as the BF_4^- salt in the concentration range 9.32×10^{-5} to 4.65×10^{-3} M was linear ($\Lambda_0 = 178$ ohm^{-1} cm^2 equiv^{-1}).[12] The observed and calculated slopes for Et_4NBF_4 and the complex were 345 (obsd) 373 (calcd) and 606 (obsd) 701 (calcd), respectively. The conductance data and electrochemical n values (0.93-0.97) taken with the analytical results indicate that **3** is a 1:2 electrolyte and must thus be composed of two oxidized Ni^{II}[14]12eneN$_4$ units.

Detailed electrochemical studies show that the dimerization process is rapid. If the $0 \rightarrow +1$ couple is studied using cyclic voltammetry, the peak to peak separation is large, ~850 mV, and scan rate dependent. However, in-phase ac polarography shows this process to be electrochemically reversible with an $E_{1/2}$ of 0.43 V and a peak width at half height of 92 mV. Carrying out the redox process at 30 Hz does not allow the π-cation radical which is initially formed to dimerize before it is electrochemically reduced.

The proposed structure of the dimer is supported by IR and ^1H NMR data. The IR spectrum of the complex shows strong bands at 1635 and 1528 cm^{-1} (Nujol mull) which are associated with the isolated imine and diiminate framework of **3**, respectively. However, the most useful structural data can be