reagent solution was forced by nitrogen pressure through a cannula which was cooled to −78 °C into a solution containing 1 molar equiv of arsenic trichloride in THF at −100 °C. The 1,1-dichloroethyldichloroarsine thus prepared was not isolated. Instead, the solution containing this material was cannulated (cooled to −78 °C) into a solution of 2 molar equiv of dicobalt octacarbonyl in THF at −78 °C. (For best results, a dilute solution (1000 ml of THF/100 mmol) of the carbonyl should be used.) When the resulting mixture was allowed to warm slowly, a vigorous evolution of gas commenced at 0 °C and subsided after 15 min. After 24 h at room temperature, it was evaporated at reduced pressure and extracted with pentane. Removal of pentane left a red oil which was chromatographed (silicic acid) to give $(CH_3CAs)Co_2(CO)_6$, an orange oil (27% yield, based on 1,1-dichloroethane), which could be short path distilled at 40 °C (0.02 Torr). Anal. Calcd for $C_8H_3O_6AsCo_2$: C, 24.77; H, 0.78; As, 19.32. Found: C, 24.97; H, 0.89; As, 20.39. In the mass spectrometer (70 eV) the complex underwent stepwise loss of CO, and fragment ions at *m/e* corresponding to $(CH_3CAs)Co_2(CO)_n^+$ (n = 0-5) were observed. Its ^1H NMR spectrum (in CCl_4) showed δ_{CH_3} at 3.13 ppm, and its infrared spectrum showed three bands in the terminal carbonyl region at 2100, 2060, and 2030 cm^{-1}, which are consistent with the presence of the $Co_2(CO)_6$ unit. Treatment of the product, Va, with 2 equiv of triphenylphosphine in refluxing benzene gave the crystalline 1,2-bis(triphenylphosphine) substitution product, $(CH_3CAs)Co_2(CO)_4(Ph_3P)_2$, which apparently is a mixture of the two possible 1,2 isomers since its ^1H NMR spectrum showed two CH_3 resonances. A 1:1 reaction of Va and triphenylphosphine at room temperature for 48 h gave the nicely crystalline monotriphenylphosphine substitution product, mp 121-122 °C. As expected, δ_{CH_3} of these complexes depended on the degree of triphenylphosphine substitution. In the ^1H NMR spectrum of the monotriphenylphosphine adduct, δ_{CH_3} was observed at 2.43 ppm (in $CDCl_3$); in the spectrum of the bis(triphenylphosphine) adduct the two methyl resonances were observed at δ 1.62 and 1.82 ppm (in $CDCl_3$).

A similar procedure in which α,α-dichlorobenzyllithium[15] was used gave 2-phenylarsaacetylenedicobalt hexacarbonyl, Vb, an air-stable red oil, in 28% yield based on starting benzotrichloride. Its mass spectrum showed the molecular ion, fragment ions with *m/e* corresponding to products of successive CO loss, $[M - CO]^+$ through $[M - 6CO]^+$, as well as $PhCAsCo^+$ and Co^+. Three $\nu_{C\equiv O}$ bands were observed at 2090, 2060, and 2035 cm^{-1}. A crystalline 1,2-bis(triphenylphosphine) substitution product could be prepared.

In the ^{13}C NMR spectra of Va and Vb (in $CDCl_3$) the resonances due to the carbon atoms in the $CAsCo_2$ cluster were observed at δ_C 170.4 and 165.9 ppm, respectively. In comparison, the cluster carbon atom resonances in the $RCCo_3(CO)_9$ and $(RC_2R(Co_2(CO)_6$ complexes were found in the ranges δ_C 275-310[16] and δ_C 91-95[17] ppm, respectively.

These $(RCAs)Co_2(CO)_6$ complexes appear to be chemically quite robust. Both are air stable. The phenyl derivative Vb may be para-acetylated in quantitative yield by adding it to a solution of acetyl chloride and aluminum chloride in dichloromethane, a procedure which served well in the acetylation of $(PhC_2Ph)Co_2(CO)_6$[18] and $PhCCo_3(CO)_9$.[19] The product, Vc, was isolated as a red oil but could be converted to a crystalline 1,2-bis(triphenylphosphine) derivative. Attempted methylation of the arsenic atom in Vb with methyl fluorosulfonate, a powerful alkylating agent, and attempted reactions of Va with $(OC)_5Cr{\cdot}THF$ and of Vb with $(OC)_5W{\cdot}THF$ were unsuccessful.

Since these $(RCAs)Co_2(CO)_6$ complexes may be regarded as derivatives of the as yet unknown arsaacetylenes, $RC{\equiv}As$,[20] it seemed possible that their thermolysis might release this species. However, thermal decomposition of Vb at 200 °C in the presence of tetraphenylcyclopentadienone did not give the hoped-for pentaphenylarsabenzene. Instead, the decomposition of Vb resulted in the formation of a shiny black mirror on the walls of the flask which was identified by analysis as Co_2As. Oxidation of Vb with ceric ammonium nitrate in methanol solution resulted in C-As bond cleavage, the organic products which were isolated being $C_6H_5CO_2CH_3$ and $C_6H_5C(O)CO_2CH_3$.

Our synthesis of Va and Vb should be capable of extension to other cluster complexes of general type IV, and such hybrid clusters should have interesting properties and chemistry. Applications to systems of type IV where M is an element other than arsenic are under investigation.

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Structure of Antibiotic X-14547A, a Carboxylic Acid Ionophore Produced by *Streptomyces antibioticus*, NRRL 8167[1]

Sir:

Of the 30 structurally defined carboxylic acid ionophores[2] known as polyether antibiotics,[3] only A23187[4] contains nitrogen. A second example, designated X-14547A, is reported here.

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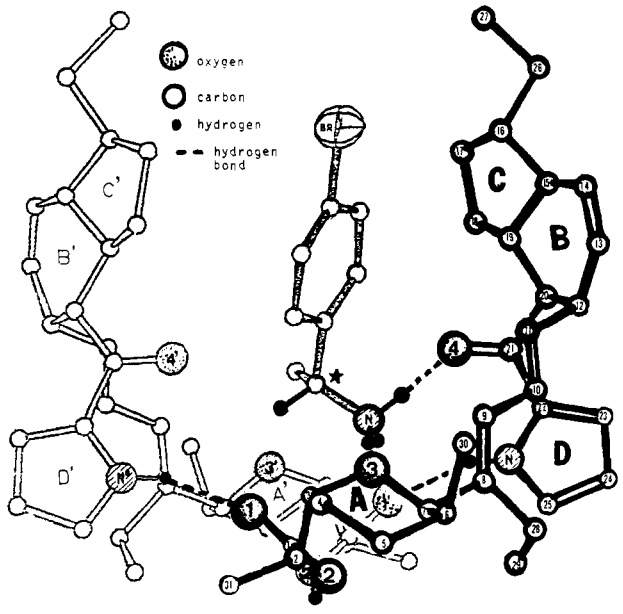
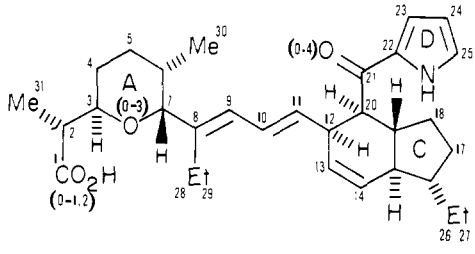


Figure 1. Structure of antibiotic X-14547A (**1**) and conformation in the crystalline state of the salt complex consisting of two antibiotic molecules and one molecule of *R*-(+)-1-amino-1-(4-bromophenyl)ethane.

As part of a search for new antibiotics possessing ion transporting properties, fermented cultures of *Streptomyces antibioticus* were filtered and the crude methanol extract from the cells was resolved by silica gel chromatography into five metabolites. One of the two major products from the fermentation was antibiotic X-14547A which was subsequently identified as $\alpha(R)$,5(*S*)-dimethyl-6(*R*)-{1-ethyl-4-[4(*R*)-(2-pyrrolylcarbonyl)-1(*S*)-ethyl-3a(*R*),5(*R*),7a(*R*)-tetrahydroindan-5-yl]-1(*E*),3(*E*)-butadienyl}tetrahydropyran-2(*R*)-acetic acid (**1**). The second major metabolite was pyrrole-2-carboxylic acid which is a frequently encountered microbial metabolite.[5] Of the three minor products, one was a novel indolone, 3-ethyl-1,3-dihydro-3-methoxy-2*H*-indol-2-one (**2**), which melts at 179 °C, and the other two were the homologous iso acids 14-methylpentadecanoic and 15-methylhexadecanoic acid which have been isolated earlier[6] as products from the Gram-positive bacterium, ***Bacillus subtilis***.



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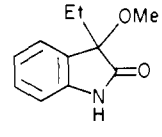

2

Antibiotic X-14547A ($C_{31}H_{43}NO_4$, mol wt 493.7) has mp 138–141 °C, $[\alpha]_D$ −328° (*c* 1, $CHCl_3$), $\nu_{max}^{CHCl_3}$ 1735, 1710 (CO_2H), 1650 (C=C—C=O), and 1627 (C=C) cm^{-1}, pK_a' = 7.12 (50% aqueous 2-propanol), and exhibits UV max at 292 nm (ϵ 12 500) and 245 (24 000). The ^1H NMR spectrum indicated the presence of four methyls at δ 0.76, 0.82, 0.9, and 1.2, five methines at 2.98, 3.35, 3.4, 3.9, and 4.2, three pyrrole protons at 6.21 and 6.91 (2 H), and two exchangeable protons at 9.45 (CO_2H) and 10.48 (NH). The number of carbons in X-14547A (**1**) was determined by ^{13}C NMR which showed 31 carbon signals when analyzed in CH_2Cl_2 solution.

The complete structure of antibiotic X-14547A was determined by X-ray analysis. Unlike the polyethers solved earlier, such as monensin[7] and lasalocid[8] where the heavy-atom salts, Ag^+ and Ba^{2+}, were analyzed by X-ray, or A23187[4] and X-206[9], analyzed as free acids, the structure and absolute configuration of X-14547A was determined from a crystal of the (*R*)-(+)-1-amino-1-(4-bromophenyl)ethane salt, mp 128–131 °C, $[\alpha]_D$ −303° (*c* 1, $CHCl_3$) (Figure 1). The salt had been prepared as part of an investigation into the resolving power of lasalocid[10] and related antibiotics toward asymmetric amines. Clearly, a cation containing an asymmetric carbon of known configuration makes the assignment of the asymmetric centers present in the antibiotic a considerably easier task than is normally the case.

A unique aspect of the (*R*)-(+)-1-amino-1-(4-bromophenyl)ethane salt of X-14547A is the 2:1 stoichiometry found for antibiotic:amine in the salt complex, although the antibiotic is a monocarboxylic acid and the amine is monobasic.

Crystals of the bromophenethylamine salt of **1** are tetragonal, space group $P4_32_12$, with a = 15.456 (2), c = 30.526 (8) Å, and four $2[C_{31}H_{43}NO_4]\cdot C_8H_{10}NBr$ dimers per unit cell. The dimers are located on the crystallographic twofold axes. The two molecules of **1** comprising the dimer are related by the twofold axis but the bromophenethylamine molecules are statistically disordered through the crystal. In each dimer there is one carboxyl group and one carboxylate group, and the oxygen and hydrogen atoms of these groups are the only atoms of **1** which are disordered.

The intensity data were measured on a Hilger–Watts diffractometer (Ni filtered Cu Kα radiation, θ–2θ scans, pulse height discrimination). Of the 2929 independent reflections for $\theta < 75°$, 2154 were considered to be observed [$I > 2.5\sigma(I)$]; the data were corrected for absorption. The structure was solved by a multiple solution procedure[11] and the final refinement was by block diagonal least squares in which the matrix was partitioned into five blocks. In the final refinement anisotropic thermal parameters were used for the nonhydrogen atoms of the molecule of **1** and the bromine atom, and isotropic temperature factors were used for the other nonhydrogen atoms of the phenethylamine and all hydrogen atoms. The hydrogen atoms were included in the structure factor calculations but they were not refined. The final discrepancy indices were R = 0.107 and wR = 0.128 for 2154 observed reflections. The relatively high R values were due to mechanical problems with the diffractometer. The problem was not discovered until well after the experiment was completed and the structure had been fully refined.

In addition to the unusual stoichiometry of the amine salt, there are two structural elements in antibiotic X-14547A that have not been observed in any of the other polyether antibiotics. One novel feature is the 1(*E*),3(*E*)-butadiene system encompassing carbons 8 to 11 in **1**, the first example of a diene in this class. The other unusual structural feature is the first example to be reported of a trans fused tetrahydroindan from natural sources, making the mechanism for the biosynthesis of the bicyclic system (rings B and C in Figure 1) of considerable interest. Part of the molecule, **1**, more characteristic of the polyethers is ring A which is identical with the analogous ring in salinomycin.[12] Another part of the the molecule found also in the first nitrogen containing ionophore of the class, A23187,[4]

is the pyrrolyl chromophore referred to as ring D in Figure 1.

From the Figure 1, the "dimeric" nature of the salt complex can be characterized as two antibiotic molecules forming a jaw-like structure within which the ammonium salt is bound. The amine is held within the dimer by three hydrogen bonds, to O-3 (3.11 Å) and the carbonyl O-4 (3.05 Å) of one antibiotic molecule and the carboxylate O-1′ (2.77 Å) of the second (prime) molecule. The hydrogen bonds holding the two antibiotic molecules together are from O-1 to NH′ (2.92 Å) and O-1′ to NH (equivalent to the former by the twofold axis) and a third between the two other carboxyl oxygens, O-2 and O-2′ (2.40 Å, an unreliable value owing to the disorder of these oxygen atoms). The 2:1 stoichiometry of the complex results from only one of the molecules of X-14547A (prime in Figure 1) being ionized in the complex, allowing the two O-2 oxygens to be hydrogen bound via the proton on the nonionized carboxyl OH.

The indication from earlier experiments in the polyether class is that the formation of dimeric complexes in the crystalline state is accompanied by an ability to transport divalent as well as monovalent inorganic cations and this was confirmed for X-14547A in the conventional U-tube experiment[13] by demonstrating the transport of radioactive $^{45}Ca^{2+}$ from one aqueous $CaCl_2$ solution to another through a bulk organic phase ($CHCl_3$) on addition of the antibiotic. Subsequently, the calcium salt of X-14547A was formed and crystallized as a hemihydrate, $(C_{31}H_{42}NO_4)_2Ca{\cdot}H_2O$, mp 179 °C, $[\alpha]_D$ −401° (*c* 1, $CHCl_3$). Other divalent polyether antibiotics reported previously are lasalocid,[8] isolasalocid,[14] and lysocellin,[15] but the only other known divalent pyrrole ether (using the recently proposed system of nomenclature[3]) is antibiotic A23187,[4] referred to at the beginning of the report. In addition to the free acid, the calcium salt of A23187 has been analyzed by X-ray crystallography as both an ethanolate[16] and a hydrate[17] and, unlike the polyethers, considerable conformational changes occur on going from the free acid to the salt complex in the case of that particular pyrrole ether.

Supplementary Material Available: Tables of the final positional and thermal parameters (3 pages). Ordering information is given on any current masthead page.

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Structure, Absolute Configuration, and Total Synthesis of an Acid-Catalyzed Rearrangement Product of Bicyclomycin

Sir:

Bicyclomycin (**1**), an antibiotic discovered simultaneously by two Japanese groups,[1,2] possesses a novel structure and an interesting profile of antibacterial activity.[3] The structure was determined by spectroscopic methods[4] and confirmed by X-ray crystallography which also established the *relative* configuration.[5] We report the structure, total synthesis (in racemic form), and absolute configuration of the acid-catalyzed rearrangement products (**2a,b**) of bicyclomycin and therefore the *absolute* configuration of bicyclomycin (**1**).

Our efforts on the total synthesis of **1** prompted us to investigate the stability of the antibiotic under acidic conditions.[6] Heating bicyclomycin in 0.1 N perchloric acid at 100 °C resulted in rapid (~15 min) conversion of the antibiotic into a less polar substance which was the main reaction product. It was isolated in 33% yield by means of chromatography and crystallization.[7] Although only one spot appears on TLC (15% EtOH/$CHCl_3$), the product (**2a,b**) obtained was a mixture of two diastereomers (~1:1) as shown by the doubling of almost every signal in the NMR spectrum.[8]

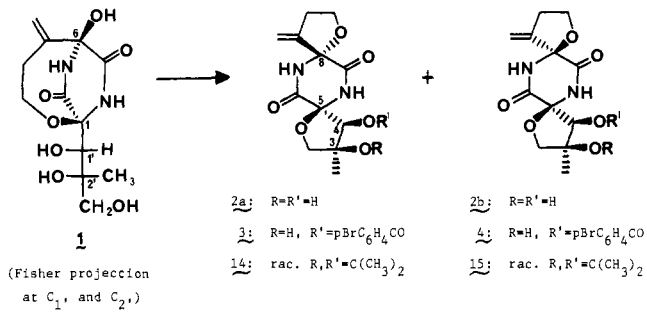
Structures **2a** and **2b** were assigned to the two diastereomers on the basis of a comparison of their NMR, IR, and mass spectra, together with TLC behavior, with those of racemic material obtained independently by total synthesis.

Thus far we have been unable to separate the two diastereomers. However, when the mixture was converted to the *p*-bromobenzoates **3** and **4** (*p*-BrC_6H_4COCl, 4-$(CH_3)_2NC_5H_4N$, dioxane, $(i\text{-}Pr)_2NEt$, room temperature, 72%), the products could be separated by preparative TLC (1:1 C_6H_6/EtOAc, three developments). Suitable crystals of the trans isomer **3** for a single-crystal X-ray diffraction analysis were obtained by crystallization from chloroform/hexane.[9] The structure was solved by Patterson and Fourier methods and was refined by full matrix least squares using 1785 reflections ($R = 0.042$, $wR = 0.053$). The absolute configuration was determined by carrying out two refinements, one using the correct value of the imaginary part of the anomalous dispersion correction for bromine ($\Delta f''$) and the other one using $-\Delta f''$. Compound **3** (as depicted in Scheme I) has the 3*S*,4*S*,5*S*,8*R* configuration. Stereodrawings are shown in Figure 1. Compound **4** is accordingly assigned the 3*S*,4*S*,5*S*,8*S* configuration. These results in turn establish the absolute configuration of bicyclomycin as 1*S*,6*R*,1′*S*,2′*S* using the numbering system employed by the earlier investigators.[4]

The rearrangement products **2a,b** were synthesized in racemic form as shown in Scheme II.

N,*N*-Diacetylglycine anhydride[10] (**5**) was condensed with the aldehyde **6**[11] using conditions reported by Gallina and Liberatori[13] (*t*-BuOK, DMF, 5 °C) to give **7**[14] in 66% yield. Hydrazinolysis ($H_2NNH_2{\cdot}H_2O$, DMF, 99%) removed the remaining *N*-acetyl group and trans ketalization conditions

Scheme I



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