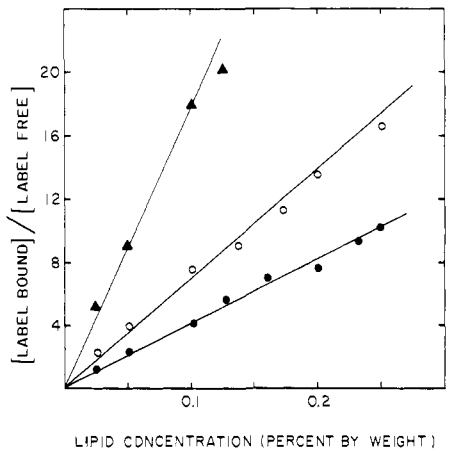

Figure 2. Binding at 27 °C of **1** vs. lipid concentration for egg lecithin plus 0% (●), 5 mol % (○), and 10 mol % cardiolipin (▲). Cardiolipin bears two negative charges/molecule.

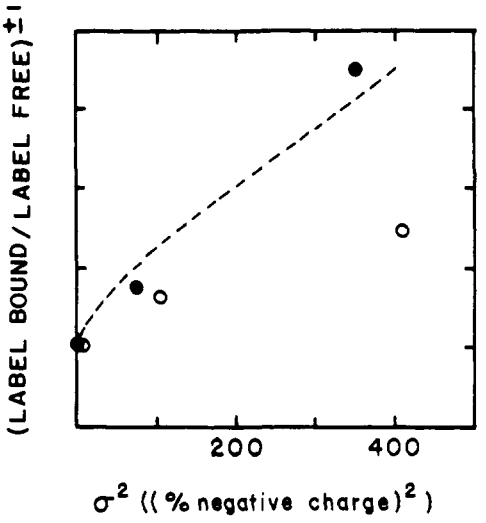

Figure 3. Normalized slopes of the type of plot shown in Figure 2 vs. σ^2, for label **1** (closed circles) and label **2** (open circles). Data are corrected for surface charge imparted by bound label. Dashed line is binding calculated for 60 Å^2/molecule.

$F\Psi/2RT = \sinh^{-1} x$ ($x = \sqrt{\sigma^2\pi/2\epsilon RT \sum_i c_i}$ for monovalent electrolytes of concentration c_i; σ = surface charge density; ϵ = dielectric constant of medium). With $\sinh^{-1} x = \ln(x + \sqrt{x^2+1})$ eq 1 becomes:

$$\text{label bound/label free} = k(x + \sqrt{x^2+1})^{\pm 2} \qquad (2)$$

For negatively charged lipid, the positive exponent applies to label **1** and the negative exponent to label **2**.

Figure 3 shows that the distribution of label **1** vs. σ^2 (filled circles) agrees well (within the limits of uncertainty of area/molecule) with binding calculated from eq 2 for a bilayer with 60 Å^2/molecule (dashed line). Label **2** binding falls below the theoretical curve and may indicate that the labels are not completely ionized in the membranes. (Label **2**, unlike **1**, does not give linear plots of the type shown in Figure 2 until buffer concentration ≥0.05 M.)

As predicted in eq 2, the binding of **1** to red blood cell ghosts is linear with $1/\sum_i c_i$ over a 20-fold concentration range. Lipid fluidity affects k in eq 2 in the same direction for both labels:[8] rigidity imparted by cholesterol decreases the bound/free ratio and sonication produces a slightly enhanced ratio.

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References and Notes

(1) **1** = 2-(7-trimethylammoniumheptyl)-4,4-dimethyl-2-octyl-3-oxazolidinyl oxyl (synthesis to be reported later). **2** = 2-(6-carboxyhexyl)-4,4-dimethyl-2-octyl-3-oxazolidinyl oxyl (W. L. Hubbell and H. M. McConnell, *J. Am. Chem. Soc.*, **93**, 314 (1971)).
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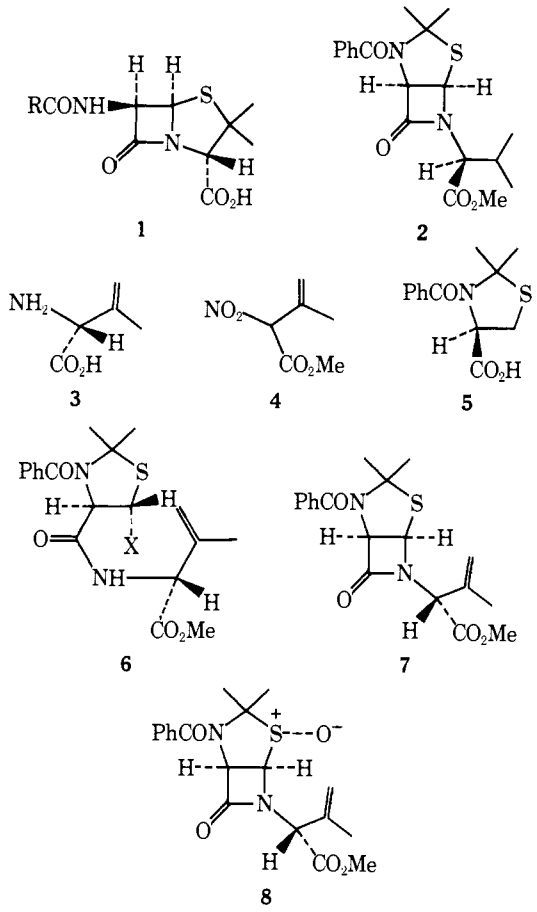
Stereospecific Synthesis of Penicillins. Conversion from a Peptide Precursor

Sir:

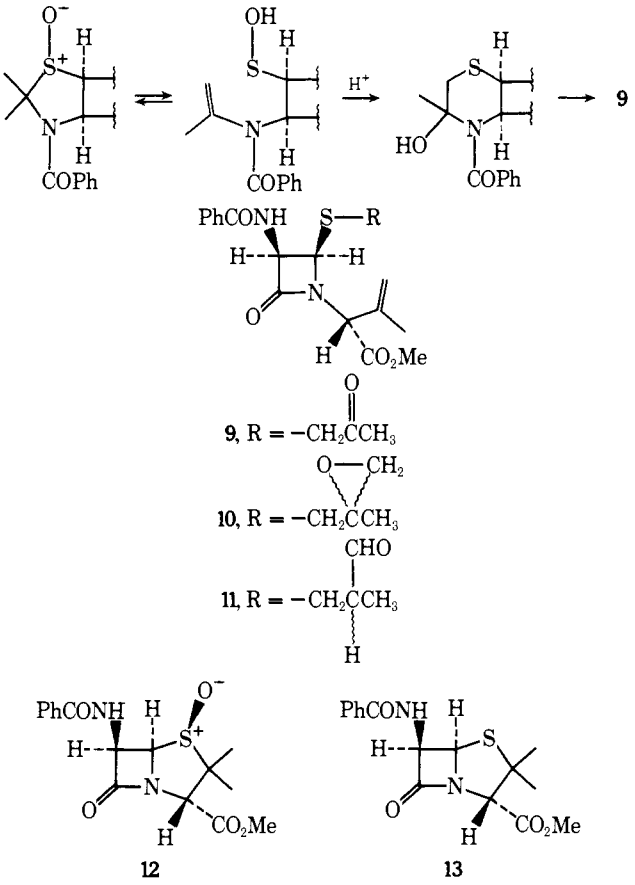
The antibiotic penicillin **1**[1] is a remarkable substance, both therapeutically and chemically. One of the more notable aspects of its chemistry, which is perhaps less well recognized, is the paucity of successful total syntheses of this molecule. At present the literature contains four claims,[2-4] none of which represents a stereocontrolled synthesis.[5] On the other hand, the less strained cephalosporin molecule and its derivatives have been the target of a number of successful stereospecific syntheses.[6-11] The existence of this situation undoubtedly results from the coincidence within the penicillin molecule of both ring strain and a very high concentration of functionality. We now present the first stereocontrolled total synthesis of a penicillin system.

Recently we described a stereospecific conversion of a dipeptide into β-lactam systems, for example **2**.[12] An extension of the original scheme[12] has now enabled conversion of a dipeptide into a penicillin, as follows. In order to close the thiazolidine ring in derivatives of **2** we required a suitably functionalized valine unit. We chose D-isodehydrovaline (**3**), which was readily obtained from methyl 2-nitrodimethylacrylate by deconjugation of the potassium salt (potassium hydride, THF, 0°) with aqueous hydrochloric acid to the β,γ-unsaturated ester **4** (at 0°, bp 115-116° (24 mm), 96%)[13] which was reduced with tin/hydrochloric acid at 95° to racemic **3** (mp 206-208° dec, 74%). Resolution of the chloroacetyl derivative of **3** with hog acylase 1, (Sigma Chemical Co.), gave, after hydrolysis (hot aqueous HCl) D-isodehydrovaline (**3**) (mp 202-205° dec, $[\alpha]^{27}$D −104.7° (*c* 3, H_2O) 60%).[14] This was coupled, as its methyl ester, with the thiazolidine acid **5**[12] (EEDQ, quinoline, CH_2Cl_2, 0°) to the dipeptide **6** (X = H, mp 185-186°, $[\alpha]^{27}$D −177.3 (*c* 1.1, $CHCl_3$), 28%). Stereospecific functionalization α to the sulfur atom was achieved with benzoyl peroxide (carbon tetrachloride, reflux) to the benzoate **6** (X = OCOPh, mp. 179-181°, 40%), which on treatment with hydrogen chloride (CH_2Cl_2, 0°) gave the chloride **6** (X = Cl, mp 137-138° dec, $[\alpha]^{28}$D −39.2 (*c* 1.2, $CHCl_3$), 94%). The stereochemistry of this series was proved by the NMR spectra. For example, in **6** (X = Cl) the coupling constant between the two vicinal thiazolidine protons was 0 Hz; a rationale for this has been previously presented.[12]

Closure of **6** (X = Cl) to the β-lactam was achieved smoothly with NaH in CH_2Cl_2/DMF at 0° yielding **7** (oil, purified by chromatography on silica gel; 82%, $[\alpha]^{27}$D −309° (*c* 2.6, $CHCl_3$); NMR δ 5.53 and 5.73 (2 H, AB quartet, J = 5 Hz); ν_{max} ($CHCl_3$) 1769, 1740, 1655 cm^{-1}), which was ox-



Scheme I



idized (*m*-chloroperbenzoic acid, CH_2Cl_2, −78°) to a single sulfoxide, believed to be the α-epimer **8** (oil; 67%, $[\alpha]^{27}D$ −229° (*c* 3.2, $CHCl_3$); NMR δ 5.27 (1 H, d, *J* = 4.5 Hz), 5.8 (1 H, d, *J* = 4.5 Hz); ν_{max} 1780, 1740, 1660, 1065 cm^{-1}). Ring opening was achieved by heating **8** in benzene/dimethylacetamide with concentrated sulfuric acid (400 M%) at 105° to yield the ketosulfide **9** (oil; 41%; $[\alpha]^{27}D$ −88.8° (*c* 0.8, $CHCl_3$); NMR δ 2.18 (3 H, s), 3.37 (2 H, s), 5.31 (1 H, d, *J* = 4 Hz) 5.62 (1 H, dd, *J* = 4, 8 Hz) 7.22 (1 H, d, *J* = 8 Hz); ν_{max} 3420, 1770, 1740, 1715, 1670 cm^{-1}). Presumably this process involves the sequence shown in Scheme I.

Generation of the required sulfenic acid moiety from **9** to effect ring closure[15] to the penicillin sulfoxide **12** was achieved by a sequence involving first transformation (CH_2N_2, methanol/ether, 0°) of **9** to the epoxide epimers **10** (oil; 53%; NMR δ 1.33 (3 H, s), 2.42-2.78 (4 H, m), 5.4, 5.42 (1 H, 2d, *J* = 5 Hz), 5.66, 5.68 (1 H, 2dd, *J* = 5, 8 Hz); ν_{max} 3400, 1765, 1745, 1670 cm^{-1}) which were smoothly rearranged (BF_3·Et_2O, THF, −30°) to the aldehyde epimers **11** (oil; NMR δ 1.06, 1.07 (3 H, 2d, *J* = 6 Hz) 5.35 (1 H, d, *J* = 4.5 Hz) 5.64 (1 H, dd, *J* = 4.5, 8 Hz) 9.63, 9.64 (1 H, 2d, *J* = 2.5 Hz); ν_{max} 3400, 1762, 1735, 1645 cm^{-1}). Oxidation (MCPBA, CH_2Cl_2, −78°) of this aldehyde pair **11**, epimeric α to the formyl group, gave the corresponding sulfoxide as a diastereoisomeric mixture (oil; NMR δ 1.3 (3 H, d, *J* = 6.5 Hz), 5.33 and 5.34 (1 H, 2d, *J* = 5 Hz), 6.39 and 6.4 (1 H, 2dd, *J* = 5, 10 Hz), 9.56 and 9.68 (1 H, 2s); ν_{max} 3350, 1780, 1740, 1670 cm^{-1}). Thermal syn elimination[15] of each of these isomeric sulfoxides from **11** can only give a single stereoisomeric sulfenic acid (along with methacraldehyde) and this reaction proceeded smoothly in refluxing benzene to yield the penicillin sulfoxide **12** (mp 161-162° dec, $[\alpha]^{27}D$ 234.0 (*c* 0.5, $CHCl_3$) in an overall yield from **10** of 21% (isolated). This substance was identical in all respects (melting point, mixture melting point, spectral data) with an authentic sample prepared from 6-amino penicillanic acid. Deoxygenation to **13** was readily achieved by means of the known procedure[16] (PBr_3, DMF, 0 °C) to yield the sulfide **13** (mp 149-151°, $[\alpha]^{27}D$ 201° (*c* 1.2, $CHCl_3$) 61%).

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Molecular Structure and Copper(II)-Mercaptide Charge-Transfer Spectra of a Novel $Cu_{14}[SC(CH_3)_2CH_2NH_2]_{12}Cl$ Cluster

Sir:

The intensely purple copper complexes of penicillamine $[HSC(CH_3)_2CHN^+H_3(CO_2^-)]$ and related ligands have possible relevance to the chemotherapeutic treatment of Wilson's[1,2] and other[3] diseases, and are a potential electronic-structural model for the Cu(II)-S(cysteine) chromophores present in the blue copper proteins. We report here the synthesis, unusual cluster structure, and selected electronic spectral properties of a complex best formulated as $([Cu^+]_8[Cu^{2+}]_6[SC(CH_3)_2CH_2NH_2]_{12}Cl)\cdot\sim3.5SO_4\cdot\sim19H_2O$ (I). A closely related complex of composition $5Tl\cdot([Cu]_{14}[SC(CH_3)_2CHNH_2(CO_2)]_{12}Cl]\cdot\sim18H_2O$ (II) was structurally characterized recently by other workers.[4]

A mixture of 1.6 g of CuO, 5.7 g of $ZnSO_4\cdot7H_2O$, 5.6 g of $HSC(CH_3)_2CH_2NH_2\cdot HCl$,[5] and 500 ml of H_2O was heated to 75 °C over a 15-min period; it yielded a gray solid and a purple filtrate. A stirred suspension of the gray solid in 300 ml of H_2O was transformed into an intensely purple solution, apparently by air oxidation (2 days, 25 °C). Addition of DMF caused precipitation of a purple solid, which was purified by three reprecipitations. Partial evaporation of a DMF/H_2O solution of the purple material yielded 2.5 g (61% based on CuO) of purple-black crystals.[6]

Diffraction data were collected on a cleaved crystal[7] using a Syntex $P2_1$ diffractometer and Mo Kα radiation. After locating the copper positions via direct methods,[8] the structure was solved and refined to convergence using 4790 reflections having $F \geq 3\sigma$; anisotropic temperature factors were refined for all Cu and S atoms. Crystal data and refinement results are as follows: monoclinic; $Z = 4$; $a = 18.318$ (3), $b = 21.826$ (5), $c = 28.829$ (6) Å; $\beta = 110.17$ (1)°; space group $C2/c$; $d_{obsd} = 1.79$ (1), $d_{calcd} = 1.745$ g/cm^3; $R_F = 9.9\%$; $R_{wF} = 13.5\%$.[9,10]

The structure (Figure 1) consists of discrete clusters in which 14 four-coordinate copper atoms are linked by 12 three-coordinate mercaptide ions and an eight-coordinate Cl^- ion[11] located at the center of symmetry. The Cl^- ion is bound in the antifluorite manner by an approximately cubic array of eight Cu atoms. The average Cl-Cu bond distance of 2.86 Å; Cu-Cl-Cu bond angles fall in the range 69.3-71.4° (70.53° is required for an idealized cubic arrangement). Four-coordination of these copper ions is completed by three triangularly oriented bonds to the bridging mercaptides; the average Cu-S (mercaptide) distance is 2.28 Å. A structural similarity of the pseudo-planar CuS_3 units to the cuprous ion sites in sulfide mineral structures[13] indicates that Cu(1), Cu(2), Cu(3), and Cu(4) are Cu(I) species. The remaining six copper atoms have an approximately planar cis S_2N_2 ligand set (indicating divalency) with average Cu-N and Cu-S distances of 2.02 and 2.28 Å, respectively. These Cu(II) species are linked via bridges composed of a Cu(I) and two mercaptide sulfur atoms. Each mercaptide bridges two Cu(I) and one Cu(II) species; average Cu(I)···Cu(I) and Cu(I)···Cu(II) distances are 3.3 and 3.9 Å, respectively. Cu(I)···Cu(I) and Cu-S distances of ~2.78 and ~2.25 Å, respectively, have been reported[14] for three Cu(I) complexes which have the Cu_8S_{12} substructure of I.

Our assignment of copper valences in I requires that the cluster have a net 7+ charge, a value consistent with the 5− charge observed for the cluster in complex II. Although elemental analysis[6] indicate the presence of $\sim3.5SO_4^{2-}$ species per cluster, only two SO_4^{2-} groups have been located crystallographically. The lattice H_2O molecules of both I and II are badly disordered; presumably, this problem also exists for some of the SO_4^{2-}.

Because the Cu(I) and Cu(II) ligand geometries differ greatly, mixed-valence transitions should require large energies[15] relative to those observed for the Cu(I)/Cu(II)-acetate system,[16] and are not expected to contribute to the visible absorptions of this rigid cluster. The broad absorption of the cluster at ~518 nm[17] corresponds to an ϵ of ~3400 per Cu(II), and is assigned to the σ-component of S → Cu(II) charge transfer (LMCT). The expected Cu(II) ligand-field absorptions may contribute to a poorly defined high energy shoulder at ~450 nm. Additional complexation of this tertiary mercaptide by two Cu(I) ions may explain the apparent absence of a weaker absorption in the 650-750-nm region otherwise expected for π-LMCT. The assignment[18] of the intense absorption at ~600 nm of the blue copper proteins to S(cysteine) → Cu(II) σ-LMCT is supported by our results. The observed blue shift of this band in the cluster to ~518 nm may result from mercaptide stabilization and/or the relatively high energy of the d vacancy in the pseudo-planar CuS_2N_2 unit. The $[Cu(I)]_2$-mercaptide unit does fall short of having thioether-like character; s(thioether) → Cu(II) σ-LMCT has been ob-

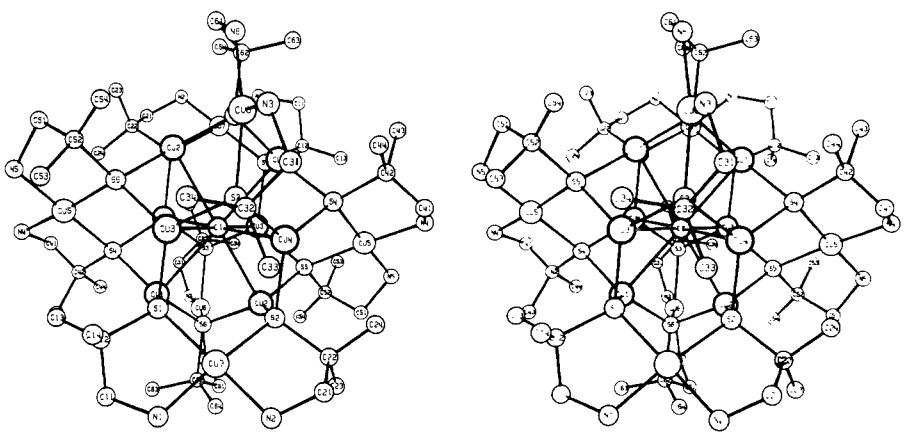

Figure 1. Stereoscopic view of $(Cu_{14}[SC(CH_3)_2CH_2NH_2]_{12}Cl)^{7+}$. For clarity the lattice H_2O and SO_4^{2-} ions have been omitted.