frothing, and after 10 min over a steam bath the slurry was treated with 10 ml of water and filtered. The precipitate which was free of boranes was discarded while the filtrate was slowly neutralized with 10% aqueous Me_4NOH. After each small aliquot of base was added, the resulting precipitate was collected and another aliquot of base added to the new filtrate. The number of solid fractions depends on the amount of Me_4NOH per aliquot. The tlc of each fraction was recorded, and those in which the same spot predominated were combined. The solubility and the R_f values both increased in the order $[Me_4N]_5B_{48}H_{45}$ (I) $< [Me_4N]_3B_{24}H_{23}$ (II) $< [Me_4N]_3B_{24}H_{22}OH$ (III) $< [Me_4N]_2B_{12}H_{12}$ (IV) $<$ $[Me_4N]_2B_{12}H_{11}OH$ (V) $< [Me_4N]_2B_{12}H_{10}(OH)_2$ (VI). The new products are described in the order that they come out of solution. They can all be recrystallized from boiling water. The yield of V was 27%, and only small amounts of IV and VI were seen; these will not be discussed as they are familiar products.[2]

The yield of crude I was 6.8 g (59%). Though R_f = 0 on PEI-F, the salt moved on silica gel when eluted with $CH_3CN-NH_4OH-H_2O$ (12:5:3). The ^{11}B nmr of compound I consisted of a doublet at δ 31.7 ppm (J = 130 Hz). The uv spectrum in CH_3CN consisted of an intense band at 2170 Å and a weak one at 2550 Å. The ir spectrum included absorptions at 3610(m), 3020(m), 2940(w), 2480(vs, B–H), 2200(s, BHB), 1600(w, H_2), 1745-(s), 1275(w), 1030(m), 1025(m), 940(s), 750(s), and 715-(s). Anal. Calcd for $[(CH_3)_4N]_5B_{48}H_{45}\cdot5H_2O$: C, 23.4; H, 11.3; N, 6.83; B, 50.6; neut equiv, 205. Found: C, 23.8, H, 11.3; N, 6.70; B, 50.2; neut equiv, 202. The neutralization curve exhibited only one sharp vertical rise indicating that the bridge protons were not titrated below pH 11.5. The Onsager plot of the conductance data for the K^+ and Cs^+ salts exhibited considerable curvature even at low concentrations so an exact value of the limiting equivalent conductance could not be obtained. However, even the lowest extrapolation yielded a molar conductance well in excess of the value expected for a 4:1 electrolyte.[3,4] The low tlc R_f value and the curvature of the conductance curve are also consistent with a very high charge on the anion. A tetrameric unit of -5 charge is the smallest that fits the analytical and conductance data.

Recrystallization of II until only one tlc spot of R_f = 0.12 was seen yielded 0.50 g (4.1%) of material, the ir spectrum and the tlc characteristics of which matched perfectly those of an authentic sample of the same compound kindly provided us by Dr. R. L. Middaugh.[3] The ^{11}B nmr consisted of a doublet, δ 33.7 ppm (J = 135 Hz). Anal. Calcd for $[(CH_3)_4N]_3B_{24}H_{23}\cdot2H_2O$: C, 26.4; H, 11.7; N, 7.77; B, 47.9. Found: C, 26.4; H, 11.5; N, 7.73; B, 47.8.

After recrystallization from water the yield of III, R_f = 0.17, was 0.20 g (1.6%). The ^{11}B nmr consisted of a singlet at δ 13.97 (area 1) and an unsymmetrical doublet at δ 33.76 (area 23, J = 130 Hz) with a shoulder at 44.17 ppm. The position of the singlet and the area ratio indicate that it represents the unique oxygen substituted boron.[2] The ir spectrum contained bands at 3620 (m), 3020 (m), 2480 (vs, BH), 2250 (m, BHB), 1600 (w, H_2O), 1480 (s), 1170 (m, BO), 1080 (m), 1040 (s), 1015 (s), 940 (s), 740 (sh), 715 (m), and 705 (m).

(4) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold, New York, N. Y., 1958, p 236.

Anal. Calcd for $[(CH_3)_4N]_3B_{24}H_{22}OH\cdot H_2O$: C, 26.7; H, 11.4; N, 7.80; B, 48.1. Found: C, 27.1; H, 11.4; N, 7.56; B, 45.3.

Oxalic acid is helpful, but not essential in this reaction. Thus when a solution of $(H_3O)_2B_{12}H_{12}$ is subjected to rotary evaporation over a steam bath until a precipitate forms, the slurry converted to a clear solution with water, and then treated with Me_4NOH, the same products are obtained but in lower yields, since a greater fraction of $B_{12}H_{12}{}^{2-}$ remains undecomposed.

Unless indicated otherwise the eluent used in our tlc work consisted of saturated NH_4PF_6, CH_3OH, and H_2O (17:2:1). The ^{11}B nmr were recorded in CH_3CN-D_2O solutions with a Varian XL-100-15 spectrometer, and the peaks are given in δ parts per million relative to trimethyl borate.

Work is currently in progress on the effects of reaction conditions on the relative yields of the reported products. We have some evidence that the "tetramer" can be decomposed to other species, but the precise nature of the decomposition products is still uncertain. We are interested in finding out whether the tetramer disproportionates to form smaller and larger units, since the "polymerization" of $B_{12}H_{12}{}^{2-}$ has been reported in the patent literature.[5] No individual components of these "polymeric" mixtures were identified, and the nature of bonding between the polyhedral units was not specified except that "boron–boron bonds" are involved; also the formulas shown do not exclude the possibility of B–O–B bridges either.

(5) U. S. Patent No. 3,350,324 (Chem. Abstr., 68, 3484 (1968)); U. S. Patent No. 3,368,878 (Chem. Abstr., 68, 105747 (1968)).

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A Revised Structure of Vermiculine. A Novel Macrolide Dilactone Antibiotic from *Penicillium vermiculatum*

Sir:

Vermiculine is a highly crystalline antibiotic substance isolated from *Penicillium vermiculatum* Dangeard.[1] The unusual medium ring lactone structure (1) was

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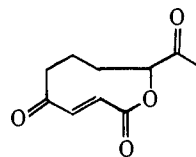
assigned on the basis of uv, ir, nmr, and mass spectral data.[2]

We had occasion to examine the chemistry of vermiculine as a prelude to an attempt at total synthesis.[3] Treatment of vermiculine with hot pyridine (80°) for 3–4 hr produced no reaction. However, treatment with aqueous methanolic sodium carbonate produced ester

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(2) P. Sedmera, J. Vokoun, M. Podojil, Z. Vanek, J. Fuska, P. Nemec, and I. Kuhr, Tetrahedron Lett., 1347 (1973).
(3) We are indebted to Dr. Jan Fuska and his associates for a most generous gift of vermiculine.

(2) after methylation. The structure was assigned on the basis of spectral data. Hydrogenation (Pd–C–ethanol) gave tetrahydro ester (3). The structure of

Figure 1. A perspective drawing of the X-ray model of vermiculine. Hydrogen atoms are not shown, and no absolute stereochemistry is implied.

3 was verified by comparison with an independently prepared sample. Ozonolysis of unsaturated ester 4[4] (methylene chloride, −78°) and reduction of the ozonide with dimethyl sulfide[5] produced the authentic sample of 3.

Reduction of vermiculine with excess zinc powder in refluxing acetic acid (6 hr) led to a crystalline acid (mp 70–72°) whose methyl ester proved to be identical with 3.

These results led us to question the proposed structure. Vermiculine had apparently undergone a remarkably facile elimination of the α-hydroxy ketone. Further, the proton nmr spectrum showed relatively few high field resonances. Examination of a molecular model of 1 suggested that marked transannular anisotropic shielding by the keto acrylate system would be expected. A search of the literature also revealed that (1) acyclic γ-keto acrylate systems undergo facile isomerization to the more stable trans form,[6] (2) the configuration of the double bond in an unsaturated carbonyl system contained in a nine-membered ring favors the cis form,[7] and (3) simple octanolides undergo rather facile hydrolysis under both acidic and basic conditions by attack on carbonyl and by nucleophilic displacement at the carbon bearing the hydroxyl group.[8] However, nmr evidence indicated the double bond to be unequivocally trans ($J \cong 16$ Hz) even after treatment with pyridine. The correct interpretation of these data was sufficiently obscure that we undertook to unambiguously establish the structure of vermiculine by a single-crystal X-ray diffraction analysis.

Vermiculine crystallizes from chloroform as clear, large cubes. The crystals belong to the orthorhombic crystal class with a unit cell of dimensions $a = 21.457(2)$, $b = 10.109(1)$, and $c = 9.021(1)$ Å. Systematic extinctions uniquely define the space group $P2_12_12_1$, and calculated and measured densities indicate one molecule of $C_{20}H_{24}O_8$ as an asymmetric unit. A total of 1537 unique diffraction maxima with $\theta \leq 57°$ were recorded using monochromated Cu Kα radiation (1.5418 Å) and a fully automated four-circle diffractometer. After Lorentz, polarization, and background correct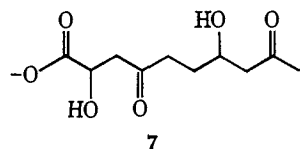ions, 1355 reflections were judged observed ($|F_o| \geq 3\sigma(F_o)$). The structure was solved by converting the observed intensities to normalized structure factors and assigning phases with a weighted multisolution tangent formula approach.[9] The best phased

three-dimensional E synthesis revealed all 28 nonhydrogen atoms. Least-squares refinement followed by a difference F synthesis showed all of the hydrogens clearly. Full-matrix least-squares refinements with anisotropic temperature factors for the carbon and oxygen atoms and fixed hydrogens converged slowly to a conventional discrepancy index of 0.037.[10] Bond lengths and angles agreed well (esd's of 0.005 Å and 0.5°, respectively) with generally accepted values.[11] See paragraph at end of paper regarding supplementary material containing bond lengths and angles and fractional coordinates. Figure 1 shows a computer drawing of the X-ray model.

The 16-membered macrocyclic ring has an approximate twofold axis perpendicular to the best molecular least-squares plane and through the center of gravity. The maximum deviation from twofold symmetry is 0.18 Å for O(1) and O(1') while the average deviation is 0.094 Å. The long sides of the roughly rectangular molecule are formed by planar arrays of atoms (O(3'), C(1), O(1), C(2), C(3), C(4), O(2), and C(5) while the twofold related atoms form the other side). The average deviation from planarity is 0.15 Å. These two planes form a sharp V with an interplanar angle of 22° and the wide opening on the O(1), O(1') side of the molecule. The greatest width of the molecule is 3.49 Å between atoms C(3) and C(1').

The revised structure for vermiculine (5) represents the first example of a dilactone in the macrolide antibiotic series. It is closely related to the antifungal agent pyrenophorin[12] which has exocyclic methyls rather than the acetonyl moiety of vermiculine. Other polylactones are nonactin and related molecules[13,14] and the acyclic portion of the antimycins.[13] The base unit for vermiculine (5) is a C-10 hydroxy diketo acid (6)

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4

5

6

which is most plausibly derived from polyacetate as is indicated by hydration of the double bond (7).[15]

7

Vermiculine (5) has the fewest asymmetric centers of any of the macrolide antibiotics. In view of vermiculine's relative simplicity and its useful antibiotic properties, studies on the possible complexation of metal ions as well as approaches to the total synthesis are currently underway in our laboratories.

Supplementary Material Available. The fractional coordinates (Table I), important bond distances (Table II), and important bond angles (Table III) will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-74-5954.

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(16) Camille and Henry Dreyfus Teacher–Scholar Grant Awardee 1972–1977 and Fellow of the Alfred P. Sloan Foundation 1973–1975.

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Stereochemistry of Oxidative Addition of Benzyl-α-d Chloride to Tetrakis(triphenylphosphine)palladium(0). Direct Evidence for Configurational Inversion at Carbon via a Nonradical Mechanism

Sir:

Oxidative addition of alkyl halides to low valent group VIII transition metal complexes may involve intermediate free carbon radicals[1,2] or occur by an

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SN2-type transition state[3–8] depending on the nature of the reactants. Recently, we reported[9] that the reaction of tetrakis(triphenylphosphine)palladium(0) (1) with α-phenethyl bromide (2) in the presence of carbon monoxide gave the acylpalladium complex 3, PhCH-(CH₃)(CO)Pd(PPh₃)₂Br, in which >90% inversion of configuration at the benzylic carbon had occurred. This stereochemistry is consistent with an initial oxidative addition of 2 to palladium, with inversion of configuration at carbon, to yield an alkylpalladium intermediate 4, PhCH(CH₃)Pd(PPh₃)₂Br, which then undergoes carbon monoxide insertion, with complete retention of configuration at carbon,[10] to afford 3. However, an attempt to isolate the alkylpalladium complex 4 from the reaction of 1 with 2 afforded only dibromobis(triphenylphosphine)palladium(II).

Recently, a nonchain radical mechanism has been proposed for the oxidative addition of methyl iodide, ethyl iodide, and benzyl bromide to tris(triphenylphosphine)platinum(0) based on the observation of the derived nitroxide radical, t-Bu(R)NO· (R = CH₃, C₂H₅, PhCH₂), in esr using $tert$-nitrosobutane as a spin trap.[11] The spin trapping results together with the failure to isolate 4 suggest the possibilities that the formation of the acyl complex 3 may involve direct nucleophilic attack by a palladium-bonded carbonyl at the benzylic carbon, and the reaction of benzyl halides with 1 in the absence of carbon monoxide may occur by a radical pathway with racemization at carbon. This communication reports the stereochemistry of the oxidative addition reaction of benzyl-α-d chloride (5) with 1 to afford the benzylpalladium complex 6, PhCH(D)Pd(PPh₃)₂Cl, and spin trapping studies of the addition of benzyl halides to 1.

Optically active (S)(+)-5[12–14] was prepared by the reaction of optically pure (S)(+)-benzyl-α-d alcohol (7)[16] with phosgene. Treatment of (S)(+)-5 with 1 in degassed benzene under nitrogen afforded the benzyl complex 6 which upon carbonylation yielded the phenylacetylpalladium complex 8. Both 6 and 8 exhibited only very small optical rotation. Bromine cleavage of 8 followed by methanolysis gave (−)-methyl phenylacetate-α-d (9), and lithium aluminum hydride reduction of the levorotatory ester 9 gave the known (R)-(+)-

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