and La^{3+} on all ^{13}C resonances unambiguously associated with rings C and D are the same within error. This absence of paramagnetic effects indicates binding is not significant in the immediate vicinity of rings C and D. (2) Paramagnetic effects of significance for rings A and B carbon signals include *marked* broadening for C_{12a}, C_4, at least one of the carbonyls C_1, C_3, or C_{11}, and less easily assessed broadening for C_2 and the amide carbon. Also a paramagnetic shift of a few hertz to lower field is observed for the amide carbon resonance. It s unlikely that the observed paramagnetic broadening in the C_1, C_3, C_{11} group occurs for C_{11}, since paramagnetic effects on neighboring signals are absent. These results then lead to the conclusion that metal binding (at least for rare earth ions in DMSO) involves ring A functional groups.

The proton NMR work strongly indicated that the ring A tricarbonylmethane group is responsible for metal binding in DMSO.[1] If such is the case, the paramagnetic broadening for C_2 and the amide carbon should be more pronounced than that of C_{12a} and C_4 using a simple $1/r^6$ dipolar broadening mechanism. The La^{3+}-induced broadening of C_2 and the amide carbon is appreciable, and it is difficult to evaluate differences between La^{3+}- and Nd^{3+}-induced broadening of these signals.[5] However, at high M^{3+}/TC ratios, broadening is definitely more severe in the presence of Nd^{3+} for both these signals. For example, the C_2 signal is clearly visible at La^{3+}/TC = 0.067 but is lost in the baseline at this mole ratio of Nd^{3+} (see Figure 1E). Although the present data cannot be used quantitatively to locate the metal ion, the conclusions drawn from proton NMR data appear to be substantiated.

The effects of Mg^{2+} on the carbon-13 NMR spectrum of TC in DMSO-d_6 were also investigated. The results parallel those of the proton NMR work in that (1) signals which broaden in the presence of Nd^{3+} or La^{3+} remain sharp at even higher Mg^{2+}/TC ratios, and (2) at high Mg^{2+}/TC ratios several new NMR signals appear concomitant with reduction in intensity of the original signals nearby.[6] The appearance of new proton NMR signals for TC in the presence of Mg^{2+} was interpreted earlier as evidence for a Mg^{2+}-induced conformational change of TC.[1] Here the new ^{13}C signals could arise from a Mg-bound conformer, but further work will be necessary to establish this.

Acknowledgments. We are indebted to Drs. G. L. Asleson and C. W. Frank for helpful discussions and for providing ^{13}C NMR signal assignments for TC. We also thank Dr. Gerald Pearson for operating the spectrometer. This research was supported by the U.S. Public Health Service through Grant No. AI-11608-01.

References and Notes

(1) D. E. Williamson and G. W. Everett, Jr., *J. Am. Chem. Soc.*, **97**, 2397 (1975).
(2) All ^{13}C NMR spectra were recorded on a Bruker HX-90-E spectrometer located at the University of Iowa. Normally 2500–3000 scans were recorded for each spectrum using a 4 μsec pulse and a 2 sec repetition time. Internal TMS was used as the reference in each case.
(3) G. L. Asleson and C. W. Frank, *J. Am. Chem. Soc.*, preceding paper in this issue.
(4) Detailed assignments for the C_1, C_3, and C_{11} signals have been made for TC·HCl in DMSO,[3] but assignments of these signals are less certain for TC free base in DMSO due to their small chemical shift differences.
(5) The C_2 and amide-C signals are broadened by La^{3+} to a larger extent than any other signals of TC. La^{3+}-induced broadening of the C_4 and C_{12a} signals is negligible.
(6) This occurs for signals assigned to the amide carbon, C_{12}, C_{11a}, and C_2.

Janet Gulbis, Grover W. Everett, Jr.*
Department of Chemistry, The University of Kansas Lawrence, Kansas 66045
Received June 26, 1975

The Vitamin D–3,5-Cyclovitamin D Rearrangement

Sir:

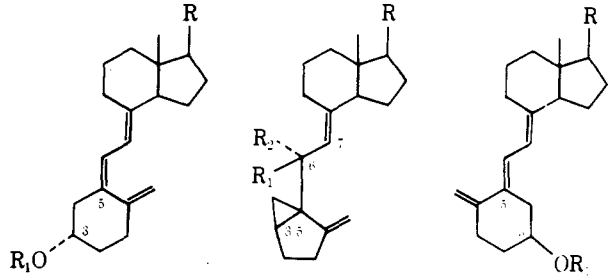
The pronounced chemical reactivity of the 1,3,5-triene system of vitamin D has considerably hampered investigation of its chemistry. The recently discovered high biological activity of vitamin D derivatives[1] induced us to search for a method to functionalize vitamin D, while protecting its reactive triene system. This report described the conversion of vitamin D_3 (cholecalciferol) to 3,5-cyclovitamins D_3 containing such a protecting system, and their stereoselective reconversion to the starting vitamin.

Heating (55°, 12 hr) of a methanol:acetone (4:1) solution of cholecalciferyl tosylate, **1b**[2,3] (1 mmol/cm^3), in the presence of NaOAc (8 equiv) yields in ca. 65% three methyl ethers, **2a, 2b,** and **1c,** in a ratio of 4.5:1:1.[4,5] The structure of the C_3-methyl ether of cholecalciferol, **1c,** was established by its uv and ^1H NMR spectra which were characteristic for the (*EZZ*)-hexa-1,3,5-triene system of cholecalciferol (**1a**) (uv, λ_{max} 264 nm, ϵ 17.000 in C_6H_{12} and in the presence of I_2, λ_{max} 272 nm;[6] ^1H NMR δ 5.08, 4.85 (=CH_2), 6.3, 6.1 ppm, AB quartet, J = 11 Hz (=C*H*—C*H*=)). The structure of (6*R*)-methyl ether, **2a,** was assigned to the major product of the solvolysis of **1b,** based on the absence in its uv spectrum of an absorption of a conjugated double bond system and on ^1H NMR evidence for the presence of two isolated exocyclic double bonds, one having two methylene protons (δ 4.89, 5.04 ppm) and the other, one methine proton vicinal to a proton on a methoxy bearing C atom (δ 4.98, 4.15 ppm, AB quartet, J = 9.7 Hz).

This structure assignment was corroborated by the off-resonance decoupled ^{13}C NMR spectrum which indicated four vinylic C atoms: two of them quaternary, one tertiary, and one secondary (δ 152.3, 143.4, 119.3, and 103.9 ppm, respectively). The configuration of C_6 was inferred both from its preponderance in the solvolysis products and from its highly stereoselective reconversion to cholecalciferol, **1a** (see below).

The third methyl ether, **2b,** is the C_6-epimer of **2a;** it shows an identical mass spectral fragmentation pattern and similar ^1H NMR spectrum to **2a** (δ 4.98, 4.81 (=CH_2), 4.69, 4.45 ppm, AB quartet, J = 8.5 Hz (OCH_3)C*H*—C*H*=)).

On acid solvolysis the cyclovitamins D_3 are reconverted to the vitamins. Thus heating (2 hr, 55°) of 75% aqueous dioxane solution of **2a** (2 mmol/cm^3) with *p*-toluenesulfonic acid (0.3 equiv) results in 80% of a mixture of cholecalciferol (**1a**) and *trans*-cholecalciferol[6] (**3a**) in 13:1 ratio.[7,8] Analogous treatment of **2b** gives also 80% of **1a** and **3a** but in a 2:1 ratio.



1a, R_1 = H
b, R_1 = Ts
c, R_1 = CH_3

2a, R_1 = H; R_2 = OCH_3
b, R_1 = OCH_3; R_2 = H

3a, R_1 = H
b, R_1 = Ts
c, R_1 = CH_3

The marked stereoselectivity in the solvolysis of cholecalciferyl tosylate **1b** (the ratio of **2a:2b** being 4.5:1) and the solvolysis of the (6*R*)-methyl ether **2a** (the ratio of **1a:3a** being 13:1) leads to the conclusion that the formation of the

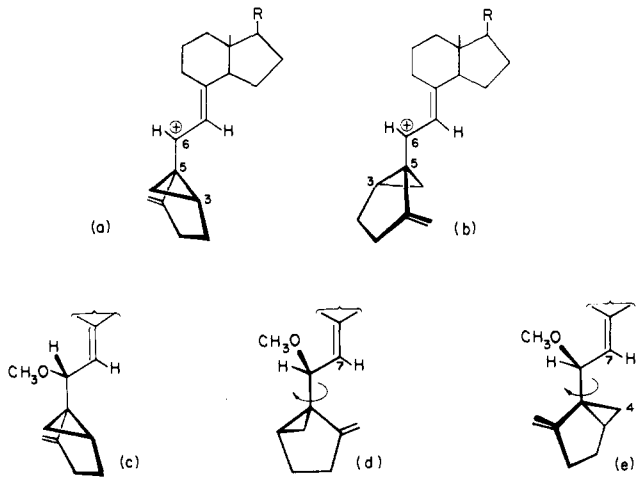


Figure 1. Perspective formulas of: (a) cyclopropylcarbinyl cation A, (b) cyclopropylcarbinyl cation B, (c) low energy conformation of (6*R*)-methyl ether **2a**, (d) low energy conformation of (6*S*)-methyl ether **2b**, (e) energetically strained conformation of (6*S*)-methyl ether **2b** with C_3-C_5 and C_6-OCH_3 bonds in antiparallel relation.

cyclopropylcarbinyl cation A (Figure 1a) from both these compounds is preferred.

We assume that the cyclopropylcarbinyl cation A has the bisected geometry in respect to the cyclopropane ring,[9] whose C_3-C_5 bond is in an anti relationship with the C_6-H bond.

The α-side attack of the methanol on the cation A (Figure 1a) is favored since it both involves C_3-C_5 bond participation and leads to the (6*R*)-methyl ether **2a** in its sterically more stable conformation (Figure 1c). In this conformation the methyl ether **2a** will also have suitable geometry for the creation of a low-energy transition state leading back to the carbonium ion A.[10]

On the other hand, the geometry of the stable conformation of the (6*S*)-methyl ether, **2b** (Figure 1d),[11] is not suitable for stereoselective formation of the cyclopropylcarbinyl cation B, whose C_3-C_5 and C_6-H bonds are in a syn relationship (Figure 1b). Conversely the transition state for a β-side attack of methanol on the cation B, which involves participation of the C_3-C_5 bond, will be less favored, since it leads to the (6*S*)-methyl ether, in its sterically strained conformation (Figure 1e).[12]

As expected, solvolysis of *trans*-cholecalciferyl tosylate, **3b**,[13] involving the intermediacy of the cation B, does not proceed stereoselectively.

Thus, heating of a solution of *trans*-cholecalciferyl tosylate, **3b** (2 mmol/cm^3), in 4:1 methanol:acetone (55°, 12 hr) yields three isomeric methyl ethers (in 60%) in a ratio of 6.5:4:1. The first two were found to be identical with (6*R*)- and (6*S*)-methyl ethers **2a** and **2b**, respectively, and the third one was the C_3-methyl ether of *trans*-cholecalciferol, **3c**, as shown by its uv and ^{1}H NMR spectra (λ_{max} 272 nm, ϵ 18.000; δ 4.96, 4.65 (=CH_2) and 6.51, 5.86 ppm, AB quartet J = 11.5 Hz (=C*H*—C*H*=)), which are typical of the (*EEZ*)-hexa-1,3,5-triene system of *trans*-cholecalciferol (**3a**).

It is to be noted that two different C_3-methyl ethers **1c** and **3c** were formed on solvolysis of cholecalciferyl and *trans*-cholecalciferyl tosylates, **1b** and **3b**, respectively, each retaining the original configuration of the tosyloxy group at C_3, confirming thus the noninterconvertibility of the cations A and B.

Acknowledgment. The authors thank Dr. Zeev V. I. Zaretskii for the mass spectra, Mr. Elisha Berman for the ^{13}C NMR spectra, and the Chemistry Department of Bar-Ilan University for the permission to use their ^{13}C NMR spectrometer.

References and Notes

(1) Cf. H. F. DeLuca, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **33**, 2211 (1974); R. M. Wing, W. H. Okamura, M. R. Pirio, S. M. Sine, and A. W. Norman, *Science*, **189**, 939 (1974), D. E. M. Lawson, D. R. Fraser, E. Kodicek, H. R. Morris, and D. H. Williams, *Nature (London)*, **230**, 228 (1971).
(2) Mp 107–108° prepared from **1a** with TsCl and pyridine.
(3) Assigned structures are consistent with their analytical data and high resolution mass spectral data, the details of which will be published later.
(4) This ratio was established by integration of the ^{1}H NMR peaks of the OCH_3 protons in the total mixture of products.
(5) In addition to these compounds, cholecalciferyl acetate (5%) and a mixture of unsaturated hydrocarbons were isolated.
(6) Due to isomerization to the *EEZ*-triene system of *trans*-cholecalciferol, **3a**; L. F. Fieser and M. Fieser, "Steroids", Reinhold, New York, N.Y. 1959 pp 146–153.
(7) This ratio was established by high-pressure liquid chromatography using Corasil II column.
(8) The remaining material consisted of a mixture of unsaturated hydrocarbons.
(9) For the review on cyclopropylcarbinyl cations see H. G. Richey, Jr., in "Carbonium Ions", Vol. III, G. A. Olah and P. v. R. Schleyer, Ed., Wiley, New York, N.Y., 1972, pp 1201–1294; K. B. Wiberg, B. A. Hess, Jr., and A. J. Ashe III, *ibid.*, pp 1295–1345.
(10) It is unlikely that *m/e* 540 is the molecular ion and that *m/e* 542 results from the addition of two hydrogens, since the absence of *m/e* 541 from the addition of one hydrogen would be most unusual.
(11) Where the cyclopropyl hydrogens are farthest from the hydrogen at C_7 and the methoxy group.
(12) In this conformation the cyclopropyl hydrogen at C_4 interacts severely with the hydrogen at C_7.
(13) On the relation between the stereochemistry of double bond formation and the conformation of cyclopropyl methyl system see M. Julia, C. Descoins, and C. Risse, *Tetrahedron Suppl.*, **8**, 443 (1966); S. F. Brady, M. A. Ilton, and W. S. Johnson, *J. Am. Chem. Soc.*, **90**, 2882 (1968); S. Sarel, J. Yovell, and M. Sarel-Imber, *Angew. Chem., Int. Ed. Engl.*, 7, 577 (1968).

Mordechai Sheves, Yehuda Mazur*
Department of Organic Chemistry
The Weizmann Institute of Science
Rehovot, Israel
Received May 1, 1975

A Revised Structure for the Antibiotic Pillaromycin A

Sir:

Pillaromycin A,[1] an antibiotic obtained from cultures of *Streptomyces flavovirens*, is composed of a tetracyclic aglycone and a highly modified monosaccharide residue.[2] As with some other previously known members of the anthracycline group of antibiotics, daunomycin[3] and adriamycin,[4] pillaromycin A displays antitumor activity. However, it is less toxic[1b]—a circumstance which is of interest in developing structure-activity relationships for this group of antibiotics. In view of this aspect, we wish to report that the structure assigned to the sugar component[5] is incorrect. Thus the formulation of the antibiotic should be **1a**, not **1b** as originally proposed.[2] In this communication we report crystallographic and mass spectral evidence in support of this claim, and in the adjoining paper,[6] synthetic studies related to this problem are described.

The structure of pillaromycin A (**1**) was unambiguously deduced from a single-crystal X-ray diffraction experiment. The crystals of composition $C_{28}H_{30}O_{11}\cdot(C_2H_5)_2O$ belong to the common monoclinic space group $P2_1$ with a = 11.097 (2) Å, b = 7.794 (2) Å, c = 17.492 (3) Å, and β = 84.58 (1)°. A total of 1947 unique diffraction maxima with $\theta \leq$ 57° were recorded using a fully automated four-circle diffractometer and graphite monochromated Cu Kα radiation (1.5418 Å). After correction for background, Lorentz, and polarization effects all reflections were utilized in subsequent calculations.

A plausible trial structure was arrived at by a multiple solution, weighted tangent formula approach[7] coupled with the recycling of plausible molecular fragments. Full-matrix,