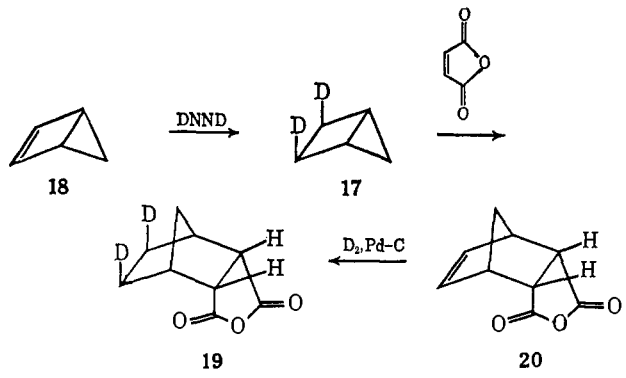

analysis by nmr.[8] The reaction of **17** with **12** was run under the same conditions as the reaction of **1** with **12**, and the *endo*-anhydride, **19**, was isolated. Within the limits of detection by nmr all of the deuterium in **19** was in the *exo* position. In order to confirm this assignment the Diels–Alder adduct of cyclopentadiene and maleic anhydride, **20**, was reduced with deuterium over palladium on carbon to yield a sample of **19** which was identical with the *endo*-anhydride obtained from **17** in all respects. In order for the deuteriums in **19** to be in the *exo* position, *the addition to bicyclo[2.1.0]pentane must have occurred from below the "flap" of the bicyclo-[2.1.0]pentane envelope.*[9]

It would appear that the initial attack by an electron-deficient carbon–carbon multiple bond on the bicyclo-[2.1.0]pentane system involves a "back-side" attack on the "bent" C_1–C_4 bond. This attack would involve an initial overlap of the electron-deficient orbitals of the carbon–carbon multiple bond with the "back orbital" of the C_1–C_4 bond, leading to homolytic cleavage with the relief of most of the strain energy of the bicyclo-[2.1.0]pentane molecule. Studies designed to further elucidate the nature of the transition state preceding diradical formation are in progress.

Acknowledgments. We are indebted to the National Science Foundation for Grant GP 7063 and to The Ohio State University Development Fund for a grant-in-aid which supported this research.

(8) P. G. Gassman and K. T. Mansfield, *J. Org. Chem.*, **32**, 915 (1967); W. R. Roth and M. Martin, *Ann. Chem.*, **702**, 1 (1967).
(9) For an example of another reaction of a substituted bicyclo[2.1.0]-pentane which was reported to occur from below the "flap" see W. R. Roth and M. Martin, *Tetrahedron Letters*, 4695 (1967).
(10) Alfred P. Sloan Research Fellow, 1967–1969.
(11) The Ohio State University Fellow, 1962–1963.
(12) National Institutes of Health Postdoctoral Fellow, 1967–1968.

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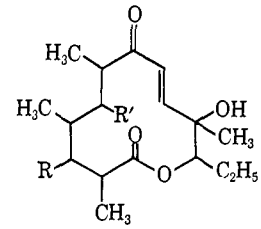
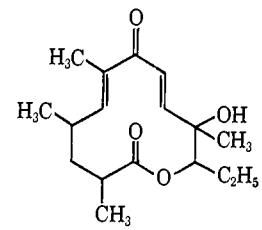
The Structure of Pikromycin

Sir:

Pikromycin was the first macrolide antibiotic[1] isolated.[2] It has long been considered to be an isomer of methymycin (**1**), which was the first macrolide of fully elucidated structure.[3] In order to account for the considerable difference in the chemical behavior of pikromycin and methymycin (**1**), structure **2** has been proposed for pikromycin[4,5] and structure **3** for its anhydro aglycone, kromycin.[4,5] Kromycin and desosamine (pikrocin) (**4**)[6] are formed upon treatment of pikromycin in water at pH 6.5.



1, R = desosamine residue; R′ = H
2, R′ = desosamine residue; R = H



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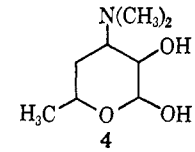
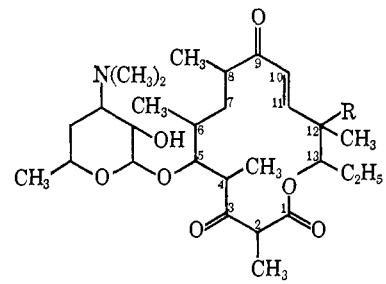
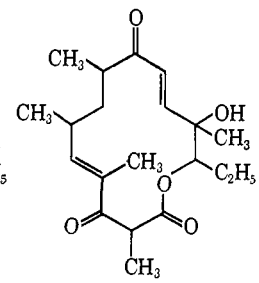


4

We now wish to report evidence that pikromycin has structure **5** and that kromycin has structure **6**. Pikromycin therefore appears to be a hydroxylated narbomycin (**7**).[7]



5; R = OH
7; R = H



6

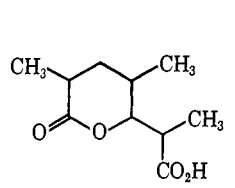
The molecular ion of pikromycin has been found at *m/e* 525 (525.3298; calcd for $C_{28}H_{47}NO_8$: 525.3302).[8] Therefore the unit C_3H_4O has to be added to the formerly accepted structure **2**.[4,5] Since kromycin has a molecular ion at *m/e* 350 (350.2093; calcd for $C_{20}H_{30}O_5$: 350.2093.), this unit has also to be added to the old structure **3** for kromycin[4,5,8] and must therefore be part of the macrocyclic ring.

It becomes evident from the nmr spectrum[9] that the C_3H_4O unit must be added to the macrocyclic ring of kromycin as shown in structure **6**. This spectrum shows a quartet with a coupling constant consistent with a proton at a carbon atom substituted by two carbonyl groups and a methyl group (1 H, δ 4.30, q, J = 6 Hz).[10]

(1) The name macrolide antibiotic was introduced by R. B. Woodward, *Angew. Chem.*, **69**, 50 (1957).
(2) H. Brockmann and W. Henkel, *Naturwissenschaften*, **37**, 138 (1950); *Chem. Ber.*, **84**, 284 (1951).
(3) C. Djerassi, and J. A. Zderic, *J. Amer. Chem. Soc.*, **78**, 2907, 6390 (1956).
(4) H. Brockmann and R. Oster, *Chem. Ber.*, **90**, 605 (1957).
(5) A. Anliker and K. Gubler, *Helv. Chim. Acta*, **40**, 1768 (1957), and preceding paper.
(6) H. Brockmann, H. B. König, and R. Oster, *Chem. Ber.*, **87**, 856 (1954); E. H. Flynn, M. V. Sigal, Jr., P. F. Wiley, and K. Gerzon, *J. Amer. Chem. Soc.*, **76**, 3121 (1954); R. K. Clark, Jr., *Antibiot. Chemotherapy*, **3**, 663 (1953).
(7) V. Prelog, A. M. Gold, G. Talbot, and A. Zamojski, *Helv. Chim. Acta*, **45**, 4 (1962).
(8) Mass spectra were taken with an MS-9 mass spectrometer. The analytical data[4,5] reported earlier are in excellent agreement with this composition.
(9) Unless otherwise stated the nmr spectra were measured in $CDCl_3$.
(10) In this region the nmr spectrum for pikromycin is not as clean as it is for kromycin because of the absorption of the desosamine moiety.

This interpretation is in agreement with the earlier finding that pikromycin when heated with 1 *N* barium hydroxide gives almost 1 equiv of barium carbonate and a "base-insoluble oil."[11]

The substitution pattern of pikromycin at C_3–C_9, as shown in **5**, and of kromycin, as shown in **6**, can be deduced from the following facts: Prelog, *et al.*, have shown that pikromycin as well as methymycin (**1**) and narbomycin (**7**) yield lactone **8** upon oxidation with potassium permanganate in acetone.[12] Furthermore,



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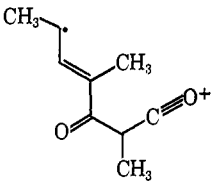

9

kromycin upon ozonolysis is degraded to pentane-2,3-dione,[4] and its high-resolution mass spectrum shows an intense peak at *m/e* 152 (152.0840; calcd for $C_9H_{12}O_2$: 152.0840), which is consistent with the ion **9**. Therefore kromycin must have a double bond between C_4 and C_5 and not alternatively between C_7 and C_8.[13] This double bond gives rise to a doublet (1 H, δ 6.30, d, J = 11 Hz) not found in the spectrum of pikromycin. In addition a methyl singlet (3 H, δ 1.90, s) has moved out of the multitude of signals between 0.88 and 1.51 in pikromycin.

Pikromycin has a double bond conjugated to a carbonyl group, as indicated by its uv and ir spectra.[4,5] This double bond, bearing two hydrogen atoms, is *trans* as shown in the nmr spectrum (2 H, δ 6.26 and 6.70; dd; J = 16 Hz). Degradation of pikromycin to kromycin leaves this double bond unchanged (2 H, δ 6.05 and 6.72; dd; J = 16 Hz). This proves the substitution pattern at C_{10} and C_{11} in pikromycin and kromycin as is shown in structures **5** and **6**, respectively.

The tertiary hydroxy group of pikromycin and kromycin[4,5] must be placed at C_{12} on the basis of chemical[5] and nmr evidence,[14] because the nmr spectrum of kromycin shows only one proton in an area characteristic for a proton bonded to carbon that bears an oxygen function. This has to be the proton at C_{13}, since it appears as a pair of doublets in the nmr spectrum (1 H, δ 4.87 and 4.93; J = 3 Hz) which is typical for a proton coupled to two diastereotopic[15] protons. This further indicates that the ethyl group of pikromycin and kromycin has to be placed at C_{13}, as already shown by chemical evidence,[4,5] *i.e.*, formation of propionaldehyde upon treatment of kromycin with sodium hydroxide and also upon oxidation of the lithium aluminum hydride reduction product of kromycin with periodic acid.

Structure **5** for pikromycin explains why pikromycin can be degraded to its anhydro aglycone, kromycin (**6**), whereas under similar conditions no defined product could be obtained from narbomycin (**7**).[16] The lactone ring in narbomycin (**7**) can be opened up by β elimination. This reaction is not possible in pikromycin because of the hydroxy group at C_{12}.

Attempts to exchange the proton at C_2 in pikromycin (**5**) and kromycin (**6**) with D_2O in chloroform–pyridine at room temperature were unsuccessful even after several days. This indicates that the macrocyclic rings of **5** and **6** are extremely rigid due to nonbonded interactions and that C_2 behaves like a bridgehead carbon atom. The rigidity of the kromycin ring shows up also in the nmr spectrum, since there is no significant difference in the nmr spectra taken at room temperature and at 160°.[17]

Acknowledgments. We are grateful to the National Institutes of Health (Grant No. FR-00355) for providing a MS-9 mass spectrometer and the National Science Foundation (Grant No. GP 6626) for general financial support. We also wish to thank Professor V. Prelog for supplying us with samples of pikromycin and kromycin.

(11) H. Brockmann and R. Strufe, *Chem. Ber.*, **86**, 876 (1953).
(12) R. Anliker, D. Dvornik, K. Gubler, H. Heusser, and V. Prelog, *Helv. Chim. Acta*, **39**, 1785 (1956).
(13) A homologous series of ions in the mass spectrum of kromycin at *m/e* 96, 109, 138, and 123 is in accord with this structural assignment.
(14) The proton of this hydroxy group appears as a broad singlet (δ 3.08) in the nmr spectrum and is easily exchanged with D_2O.
(15) K. Mislow, "Topics in Stereochemistry," Vol. I, Interscience Publishers, New York, N. Y., 1967.
(16) V. Prelog, A. M. Gold, G. Talbot, and A. Zamojski, *Helv. Chim. Acta*, **45**, 4 (1962).
(17) Nmr spectra taken in 1-chloronaphthalene.
(18) National Institutes of Health Predoctoral Fellow, 1967–present.

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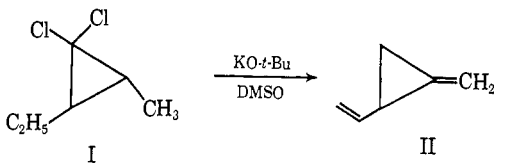
Vinylmethylenecyclopropane

Sir:

The syntheses of variously substituted methylenecyclopropanes have been reported in recent years. The thermal rearrangement of these compounds is of special interest due to the intermediacy of the trimethylenemethane system.[1] Vinylmethylenecyclopropane is of interest in this regard and, to our knowledge, has never been synthesized. We wish to report its properties and preparation *via* the useful technique of base-induced elimination–isomerization of readily obtainable *gem*-dichlorocyclopropanes.[2,3]

When 1,1-dichloro-2-ethyl-3-methylcyclopropane (I) was added slowly to a solution of potassium *t*-butoxide in dimethyl sulfoxide (1.7-hr reaction time), vinylmethylenecyclopropane (II) was obtained (62% yield)



I II

(1) W. Moffitt, *Trans. Faraday Soc.*, **45**, 373 (1949); J. D. Roberts, A. Streitwieser, Jr., and C. M. Regan, *J. Amer. Chem. Soc.*, **74**, 4579 (1952); H. H. Greenwood, *Trans. Faraday Soc.*, **48**, 677 (1952); P. Dowd, *J. Amer. Chem. Soc.*, **88**, 2587 (1966), and references cited therein.
(2) Compounds I and IV[3] were prepared from 2-pentene and 2-methyl-2-hexene, respectively, by treatment with potassium *t*-butoxide and chloroform in *n*-pentane; *cf.* T. C. Shields and P. D. Gardner, *J. Amer. Chem. Soc.*, **89**, 5425 (1967).
(3) All compounds reported gave satisfactory elemental analyses.