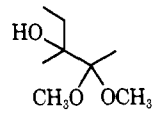
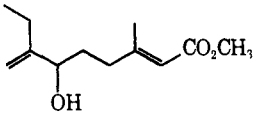
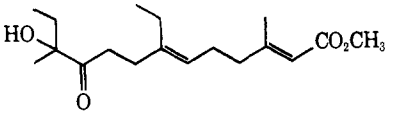
hydroxy ketal **1a** possessed the *R* configuration and had an optical purity of 92%. Using the observed rotations for the enantiomeric forms of 3-methylpent-1-yn-3-ol, the (*S*)-(+)-hydroxy ketal **1b** was calculated to have an optical purity of 85%.



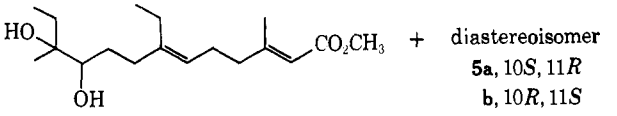
1a, $[\alpha]^{23}D$ −0.3° (*c* 3.3)
b, $[\alpha]^{23}D$ +0.3° (*c* 2.7)



2

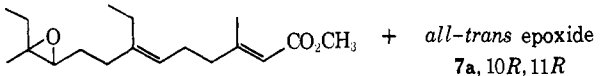


3a, b



4a, 10*R*, 11*R*
b, 10*S*, 11*S*

+ diastereoisomer
5a, 10*S*, 11*R*
b, 10*R*, 11*S*



6a, 10*S*, 11*R*
b, 10*R*, 11*S*

+ *all-trans* epoxide
7a, 10*R*, 11*R*
b, 10*S*, 11*S*

Table I. Observed Optical Rotations

Composition[a]	$[\alpha]^{23}D$, deg	Concn, g/100 ml
75% **4a**, 25% **5a**	+2.8	2.5
75% **4b**, 25% **5b**	−1.6	3.0
80% **5a**, 20% **4a**	−0.8	3.2
90% **5b**, 10% **4b**	+0.3	3.1
75% **6a**, 25% **7a**	−7.3	0.5
75% **6b**, 25% **7b**	+4.8	1.0
80% **7a**, 20% **6a**	−2.2	1.0
90% **7b**, 10% **6b**	+0.7	1.0

[a] The ratio of signals at 1.17 (trans) and 1.19 ppm (cis) in the 220-MHz nmr spectra of the epoxides in $CDCl_3$ solution.

Both enantiomeric hydroxy ketals **1a** and **1b** were allowed to react at 110° with 1.2 equiv of the hydroxy ester **2** in a solution of xylene containing 2,4-dinitrophenol. The resulting ketols **3a** and **3b**, formed *via* a Claisen rearrangement,[9] were immediately reduced using sodium borohydride in methanol solution at 0° to obtain diastereoisomeric pairs of diols **4a** and **5a** (from **1a**) and **4b** and **5b** (from **1b**), which were partially separated with great difficulty by preparative thin-layer chromatography on silica gel. The diols were allowed to react with *p*-toluenesulfonyl chloride in pyridine to form the corresponding monotosylates, which were treated with sodium methoxide in anhydrous methanol to obtain the epoxides. Thus the *threo*-diols **4a** and **4b** gave rise to the required *trans,trans,cis*-epoxides **6a** and **6b**, while the *erythro*-diols gave the *all-trans*-epoxides **7a** and **7b**. Examination of the 220-MHz nmr spectra of the product epoxides revealed that each epoxide was contaminated with its diastereoisomer.

(9) D. J. Faulkner and M. R. Petersen, *Tetrahedron Lett.*, 3243 (1969).

The observed optical rotations (Table I) must therefore be related to the approximate composition of the diastereoisomeric mixtures. There was no doubt, however, that dextrorotatory C-18 *Cecropia* juvenile hormone had been synthesized from (*S*)-(+)-2,2-dimethoxy-3-methylpentan-3-ol. Thus the natural hormone of Meyer and Hanzmann must have the 10*R*,11*S* configuration.

Acknowledgment. Financial support of this research by the National Science Foundation and the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

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The Structure of Lipoxamycin, a Novel Antifungal Antibiotic

Sir:

The production, isolation, characterization, and testing of lipoxamycin have been reported.[1] In this communication[2] we describe reactions (Scheme I) and data to support structure **1** for this new antifungal agent produced by a new strain of *Streptomyces virginiae*.

Potentiometric titration[3] of lipoxamycin sulfate ($C_{19}H_{36}N_2O_5 \cdot {}^1/_2H_2SO_4$, mp 155°) showed the presence of a basic group ($pK_a = 6.8$) and a weakly acidic group ($pK_a = 9.8$). Lipoxamycin ($C_{19}H_{36}N_2O_5$, mp 68–70°) (**1**) was obtained after the first equivalent of alkali. A positive (red) ferric chloride test is ascribed to the weakly acidic center which is in accord with an inferred hydroxamic acid group.

1 shows absorptions in the ir including NH/OH ν_{max}^{Nujol} 3150–3350 cm^{-1} and C=O at 1700 and 1640 cm^{-1}, with Nujol masking strong $-CH_2-$ and $-CH_3$ absorptions found in a melt spectrum. The pmr spectrum of **1** contains a doublet at δ 0.9 (J = 5.9 Hz) assigned to the methyls of an isopropyl grouping, aliphatic methylene multiplet at 1.3–1.8, a methylene (adjacent to carbonyl) triplet at 2.38 (J = 7.0 Hz), and unresolved resonances at 2.7, 3.8, and 4.75.

The antibiotic is very sensitive to oxidation; thus, periodic acid converts **1** to bis-1-nitrosolipoxane[4] (**2**), formulated as the *C*-nitroso dimer ($C_{32}H_{58}N_2O_6$, mp 94–96°) expected[5] from an N-substituted hydroxamic acid. **2** shows absorptions in uv and ir spectra at λ_{max}^{EtOH} 283 mμ (ε 10,360) and ν_{max}^{Nujol} 1705, 1330, 1230, 1210,

(1) H. A. Whaley, O. K. Sebek, and C. Lewis, Abstracts of Tenth Interscience Conference on Antimicrobial Agents and Chemotherapy, Oct 19, 1970.

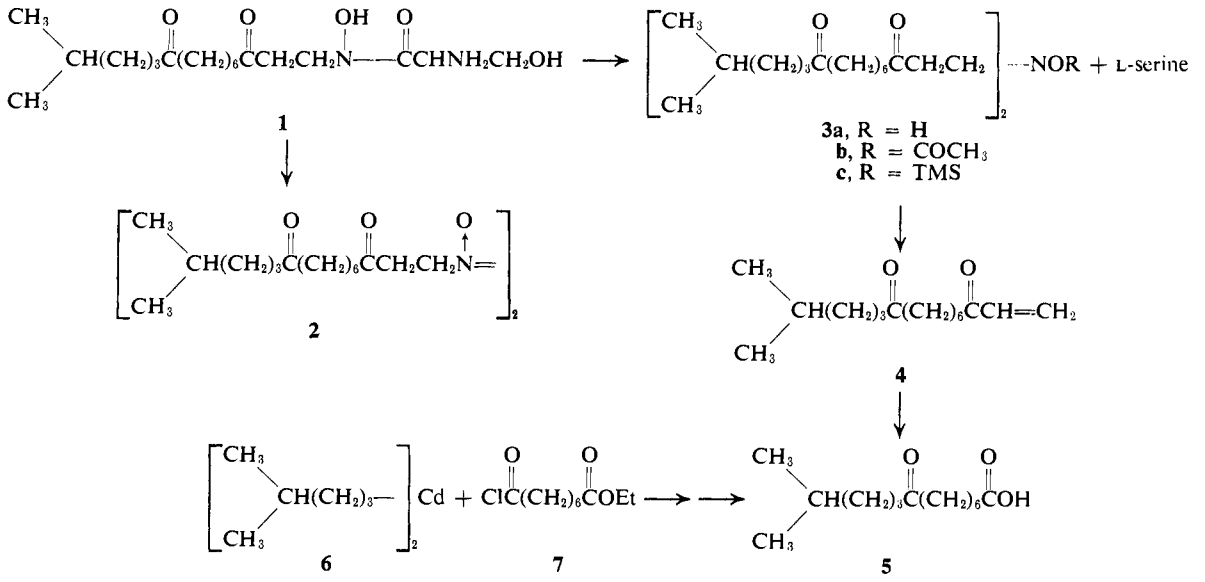
(2) Satisfactory elemental analyses were obtained for all compounds. The pmr spectra were obtained from samples in $CDCl_3$ solution using a Varian A-60, HR-60, or T-60 instrument and chemical shifts are reported in parts per million downfield from an internal tetramethylsilane. Mass spectra were obtained by electron impact in a CEC 21-110 spectrometer using the peak matching method for high-resolution ion measurement. All melting points were determined by the capillary tube method and are corrected.

(3) Because of the poor aqueous solubility of lipoxamycin sulfate, the best titration data were obtained in 60% ethanol and excess NaOH with immediate backtitration with acid: equiv wt, 209 with a break at 437; pK_a, 6.8 and 9.8.

(4) Convenient trivial names for this series of degradation products from lipoxamycin are obtained by renaming 14-methyl-3,9-dioxopentadecane "lipoxane"; then the $C_{16}H_{29}O_2$ radical derived from that can be called lipoxyl.

(5) T. Emery and J. B. Neilands, *J. Amer. Chem. Soc.*, **82**, 4903 (1960).

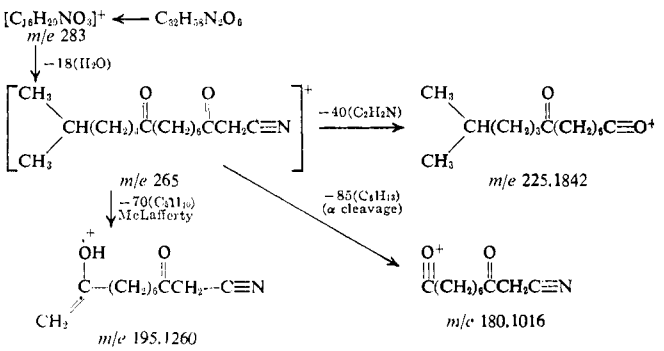
Scheme I



and 1080 cm^{-1}, respectively. The pmr spectrum of **2** shows two almost identical triplets at δ 2.95 and 4.49 (J = 6.0 Hz), assigned to the C(=O)CH_2 and CH_2-N(→O) methylene protons, respectively. These assignments were confirmed by spin-decoupling experiments. Resonances resulting from the methyl protons of the isopropyl grouping (d, δ 0.87, J = 5.9 Hz), unresolved methylenes (m, δ 1.3–1.8), and carbonyl-adjacent methylenes (t, δ 2.37, J = 7.0 Hz) are very similar to the analogous portions of the pmr spectra of **1** and most of the degradation products.

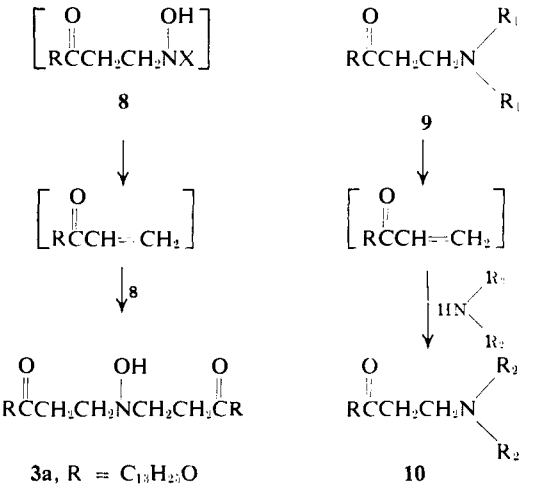
In the mass spectrum of **2**, a molecular ion of the monomer ($C_{16}H_{29}NO_3$) at *m/e* 283 is the highest mass recorded. High-resolution spectra confirm the composition of the major fragments at *m/e* 225, 195, and 180. The pattern of fragmentation is rationalized in Scheme II.

Scheme II



Treatment of **1** with alkali resulted in degradation of the antibiotic to L-serine[6] and a new compound, dilipoxylhydroxylamine ($C_{32}H_{59}NO_5$, mp 121–123°) (**3a**) containing two of the diketoalkyl chains which constitute the carbon backbone of the antibiotic. The isolation of a disubstituted hydroxylamine from this reaction is rationalized in that the structure of the lipoxamycin monosubstituted hydroxylamine derivative **8** is structurally similar to a Mannich base, **9**, both β-amino ketones (Scheme III).

Scheme III



Facile amine exchange reactions are reported for Mannich bases (**9** → **10**), owing to this functional arrangement.[7] Both reactions may be viewed as β eliminations to give vinyl ketones which react by a Michael condensation with another amine.[8] After β elimination of the lipoxamycin fragment, condensation of that fragment with a monosubstituted hydroxylamine, **8**, gives the bis derivative **3a** which precipitates, driving the reaction to completion. In the ir spectrum of **3a** are prominent hydroxyl and carbonyl absorptions at ν_{max}^{Nujol} 3170 and 1700 cm^{-1}, respectively. The pmr spectrum of **3a** is like that of **1** between δ 0.7 and 2.6 and the only other resonance in the spectrum is an apparent doublet of doublets at 2.8. Acetylation of **3a** with acetic anhydride and pyridine gave *O*-acetyl dilipoxylhydroxylamine ($C_{34}H_{61}NO_6$, mp 47–50°) (**3b**). An ir spectrum of **3b** shows no hydroxyl absorption but $\nu_{C=O}^{Nujol}$ 1760 and 1700 cm^{-1}. In the pmr spectrum of **3b** a new methyl singlet appears at δ 2.0 while methylene triplets have been shifted downfield to 3.2 and 2.65 leaving less area under the original triplet at 2.4.

(6) L configuration according to the Clough–Lutz–Jurgenson rule; see J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Wiley, New York, N. Y., 1961, p 83.

(7) J. C. Craig, S. R. Johns, and M. Moyle, *J. Org. Chem.*, **28**, 2779 (1963).

(8) For reactions of vinyl ketones with hydroxylamines to give the bis product, see D. J. Casey and C. S. Marvel, *ibid.*, **24**, 1022 (1959).

A mass spectrum of the trimethylsilyl (TMS) derivative of dilipoxyl hydroxylamine (**3c**) contained a strong molecular ion at the expected *m/e* 609 and an intense fragment ion at *m/e* 519 from loss of TMS–OH. This *m/e* 519 peak (high-resolution 519.43006 = $C_{32}H_{57}NO_4$) is the highest mass in the spectrum of the *O*-acetyl derivative **3b** resulting from an apparent loss of acetic acid to give the enamine ion, $[C_{14}H_{25}O_2CH_2\text{-}CH{=}NC_{16}H_{29}O_2]^+$. In both spectra the *m/e* 519 ion then fragments by α-ketone cleavage and β-ketone McLafferty rearrangements.

An attempt to O-methylate **3** with CH_3I in acetone and K_2CO_3 gave instead the β-elimination product **4**, which we call lipox-1-ene. Lipox-1-ene is an oil showing new vinyl ketone absorptions at ν_{max}^{neat} 1670 and 1610 cm^{-1} in its ir spectrum and vinyl protons at δ 5.7–6.4 in its pmr spectrum. A high-resolution mass spectrum showed a molecular ion at *m/e* 252.2085 ($C_{16}H_{28}O_2$) for **4**.

Periodate–permanganate oxidation of the vinyl ketone, **4**, gave the previously unknown acid, 12-methyl-8-oxotridecanoic acid (**5**). This compound was synthesized using the cadmium Grignard reagent of 1-bromo-4-methylpentane (**6**) and ω-carbethoxysuberoyl chloride (**7**). The acid **5** obtained by synthesis ($C_{14}H_{26}O_3$, molecular ion 242.1878, mp 59.5–62.3°) gave ir and pmr spectra identical with those of the acid obtained by degradation. Mass spectra of both acids show identical molecular ions and fragmentation patterns.

These data substantiate structure **1** for lipoxamycin, a novel *N*-diketoalkyl-substituted hydroxamic acid with potent antifungal properties.

Acknowledgments. We wish to thank Mrs. L. C. Davenport for technical assistance and acknowledge the aid of members of the Physical and Analytical Chemistry Department at The Upjohn Co. Helpful discussions with Professor K. L. Rinehart are also gratefully acknowledged.

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Electron Spin Resonance Studies of Equilibria in Semiquinone–Alkali Metal Ion Systems

Sir:

It has recently been suggested[1] that an endor-induced esr study of solutions of the durosemiquinone anion supports an earlier esr study of the system,[2] despite the fact that the work of ref 2 has been reinterpreted by others.[3] The purpose of this communication is to suggest that the endor work is consistent with our reinterpretation and also supports our claim that the spectra of ref 2 were incorrectly interpreted.

In our studies of semiquinone systems, we have generally found that spectra from the "free" ions[4] and

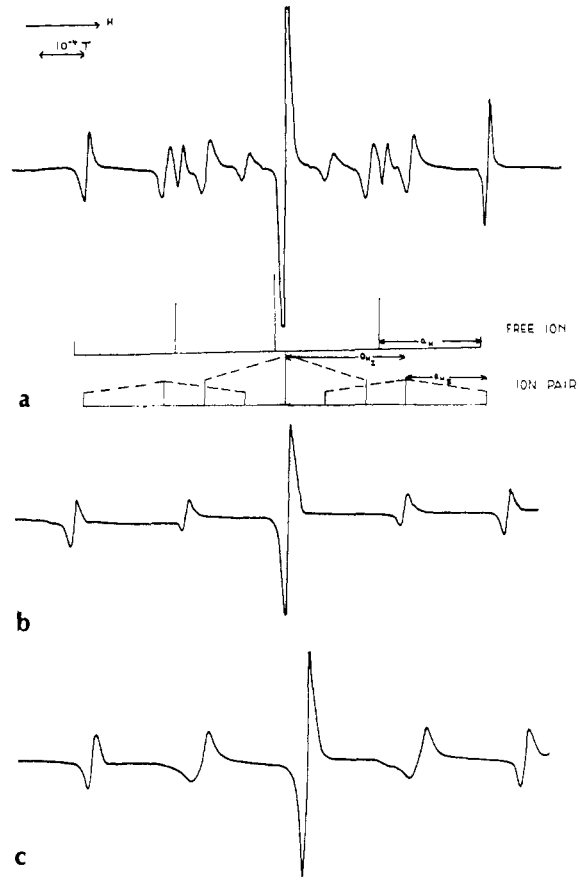

Figure 1. Esr spectra for potassium *p*-benzosemiquinone at various temperatures: (a) at 183°K, showing a quintet for the "free" anion and a triplet of triplets for the ion pair; (b) at 240°K, the "free" ion spectrum remains unchanged, but certain features of the ion-pair spectrum have broadened; (c) at 263°K, the spectrum of the "free" anion is coincident with that of the ion pair for which marked linewidth alternation is apparent.

ion pairs are detected simultaneously.[3,5,6] What *was* disputed was the suggestion[2] that a third species, possibly a solvent-separated ion pair, was also present. We have shown that *no* new spectral features were present, the effect being an unfortunate artifact.[3] The endor results confirm our conclusion.

In all our studies of alkali metal salts of *p*-benzosemiquinone,[3,5] 2,6-dimethyl-*p*-benzosemiquinone,[6] and durosemiquinone[3,5] the low-temperature spectra (~180°K) comprise narrow lines from the "free" anions and narrow lines from the asymmetric ion pairs.[3,5,6] As the temperature is raised, certain lines for the ion pairs broaden and merge to give spectra comparable with those of the "free" anion, but with alternating narrow and broad features, while the lines for the "free" anion remain narrow.

We conclude that "free" anions are not involved in the broadening process and that the rate of interconversion of the "free" anions and ion pairs is slow ($<10^6$ sec^{-1}). This reinforces our view that the normally accepted model of intramolecular oscillation of

(1) R. D. Allendoerfer and R. J. Papez, *J. Amer. Chem. Soc.*, **92**, 6971 (1970).
(2) M. P. Khakhar, B. S. Prabhananda, and M. R. Das, *ibid.*, **89**, 3100 (1967).
(3) T. A. Claxton, J. Oakes, and M. C. R. Symons, *Nature (London)*, **216**, 914 (1967); J. Oakes and M. C. R. Symons, *Trans. Faraday Soc.*, **66**, 10 (1970).
(4) These were identified as "free" or solvated anions and not solvent-separated ion pairs on the basis of (i) dilution experiments and (ii) independence of the spectrum from the counterion.
(5) J. Oakes, Ph.D. Thesis, University of Leicester, 1967.
(6) T. A. Claxton, J. Oakes, and M. C. R. Symons, *Trans. Faraday Soc.*, **64**, 596 (1968).