

REVISED STRUCTURE OF CERULENIN

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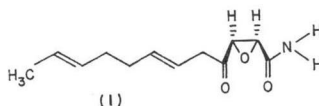
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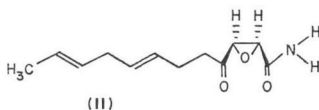
(Received for publication August 25, 1973)

An evaluation of the 100 MHz NMR spectrum strongly suggests that the structure of cerulenin is (2S) (3R) 2,3-epoxy-4-oxo-7,10-dodecadienoyl amide rather than the -6,10-dodecadienoyl amide analog. This conclusion was experimentally supported by a spin-decoupling study in a benzene-chloroform mixed solvent system.

The antifungal antibiotic cerulenin¹ has been isolated from *Cephalosporium caerulens*². Recently, it was reported that the antibiotic is a potent lipid biosynthesis inhibitor in bacteria, yeast and rat liver^{3,4,5}. From chemical degradation and spectrometric studies, structure (I) was proposed^{6,7}.

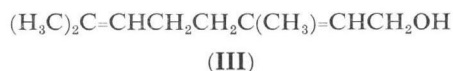


In this report we wish to describe the evidence that the double bond isomer (II) is more consistent with the NMR (100 MHz) features than structure (I).



(2S) (3R) 2,3-Epoxy-4-oxo-7,10-dodecadienoyl amide

The NMR spectrum in CDCl_3 (Fig. 1) shows that two of the three methylene groups resonate at δ 2.70 while the third occurs at δ 2.35. The multiplicity of the latter (a quartet with second order splitting) strongly suggests that it is one of the two adjacent methylenes in the molecule. Its neighbor must therefore absorb at δ 2.70. The chemical shift difference of 0.35 ppm is difficult to understand in terms of (I) since on first principles one would expect the protons on the dimethylene group to be virtually equivalent. This point is illustrated by the NMR spectrum of geraniol (III)⁸ in which the signals of the dimethylene protons are essentially coincident despite differences in the alkyl substituents attached to the individual double bonds.



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The NMR findings in benzene also pose a problem for Structure I. The most striking difference between the CDCl_3 and C_6D_6 curves involves the methylene resonances. In the aromatic solvent, two of the three methylene signals appear at δ 2.30 while one occurs at δ 2.70. This change in appearance could result merely from a selective upfield shift of one of the two methylene signals which absorbed at δ 2.70 in CDCl_3 . (This view necessitates that the remaining two methylene groups are unaffected by the solvent change). The lack of discernible fine structure in the residual methylene signal at δ 2.70 suggests that it is more likely associated with the isolated methylene group*. It would then follow that it is the lower field methylene of the dimethylene group which undergoes the solvent displacement. This, too, is surprising in terms of (I) since benzene solvent shifts normally are appreciable only for protons close to an electron deficient site^{9,10}.

In contrast to (I), the above spectral features are easily reconciled with the double bond isomer (II). Non-equivalence of the dimethylene protons in CDCl_3 would reasonably follow from the fact that the attached functional groups are different. The lower field signal at δ 2.70 is preferably assigned to the $\text{CH}_2\text{C}=\text{O}$ protons. Its relatively deshielded position can be attributed to the influence of the epoxide, and the upfield shift in benzene is consequent to its proximity to a ketone. The chemical shift of the $=\text{CHCH}_2\text{CH}=\text{}$ protons (δ 2.70) compares favorably with the analogous methylene in methyl linolenate¹¹.

Further compelling evidence for (II) was obtained from a spin-decoupling study in a CDCl_3 - C_6D_6 mixed solvent system (85% CDCl_3 ; 15% C_6D_6) in which all three methylene signals were completely resolved (Fig. 2). The solvent shifted methylene at δ 2.43, heretofore unobserved, is a triplet with second order splitting, and the intensity relationships clearly indicate that it is vicinal to the methylene near δ 2.30. The fact that its multiplicity is not the same as that of its higher field neighbor is by itself strong evidence against (I). Irradiation of the vinylic protons had no effect on this triplet thus indicating the presence of a methylene group

* Since the methylene signal at δ 2.35 (CDCl_3) showed a well-defined coupling pattern, the multiplicity of its neighbor should be equally evident.

Fig. 1. NMR spectrum of cerulenin (CDCl_3)

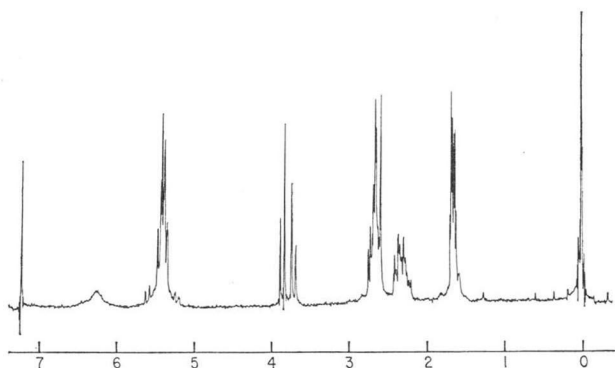
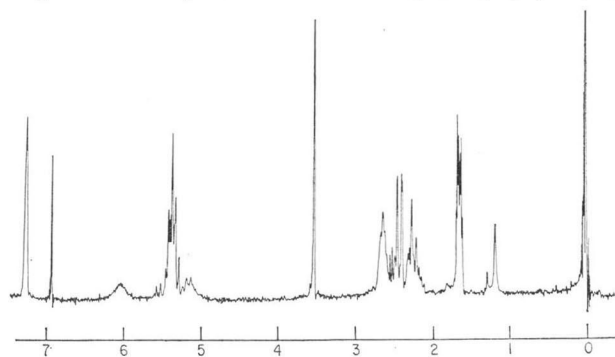
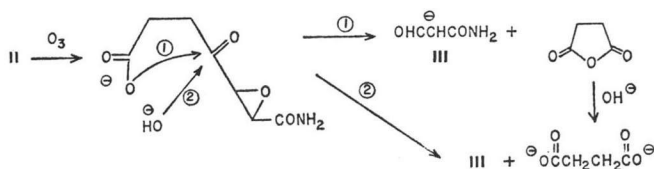


Fig. 2. NMR spectrum of cerulenin ($\text{CDCl}_3/\text{C}_6\text{D}_6$: 85/15)





in the molecule which was not vicinal to a vinylic proton. Further, irradiation of the highest field methylene collapsed the methylene triplet to a singlet. Both observed effects are compatible only with (II).

Finally, the formation of disodium succinate from (II) *via* an ozonolysis reaction can be rationalized by the above schemes*. Both require that the isolation of the oxonolysis product be carried out under alkaline conditions, as was in fact the case⁶¹.

Acknowledgement

The authors express their deep gratitude to Professor Max TISHLER, Wesleyan University for his hearty encouragement and the valuable suggestions.

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* We are indebted to Dr. RAYMOND FIRESTONE, Synthetic Chemical Research, Merck & Co., Inc. for these proposals.