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ANCEPSENOLIDE: A NOVEL BISBUTENOLIDE OF MARINE ORIGIN

Chemistry of Coelenterates. V[1]

F. J. Schmitz[2], K. W. Kraus[3], L. S. Ciereszko,
D. H. Sifford, and A. J. Weinheimer
Department of Chemistry, University of Oklahoma, Norman, Oklahoma

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The isolation of a crystalline lactone from the pentane extracts of the gorgonian *Pterogorgia anceps* (Pallas) (4) (synonymous with *Xiphigorgia anceps*) from Bimini was described in an earlier paper (1b). The results of recent chemical degradations now permit us to formulate a structure for this compound for which we suggest the name *ancepsenolide*.

Ancepsenolide was obtained from the crude extracts of *Xiphigorgia anceps* as a white solid, m.p. 91.5-92.0°, after chromatography over alumina and recrystallization from methanol.* Mass spectral analysis and combustion data established the molecular formula for ancepsenolide as $C_{22}H_{34}O_4$(m/e 362).**

The infrared spectrum of I exhibited a single intense absorption at 1745 cm^{-1} and a weak band at 1650 cm^{-1}; a maximum in the ultra-violet spectrum was observed at 208 mμ(ε = 28,000) (DK-1, N_2 atm). Saponification

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*Previously reported constants (1b) m.p. 93-94°, $[a]_D$ = 13.2° (2.8 $CHCl_3$). In the present work samples exhibiting variable small optical rotations, both positive and negative, were encountered. All the samples appeared to be homogeneous as judged by TLC and NMR and were found to be identical by virtue of mixed melting points as well as IR, UV and NMR spectra.

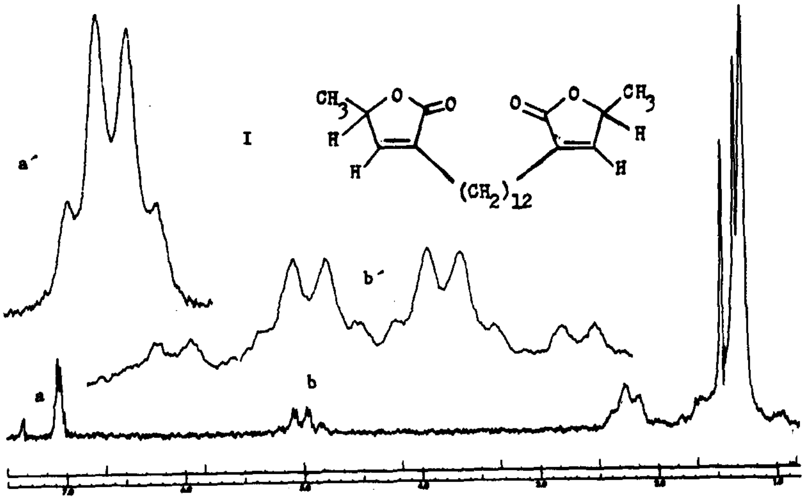
**Satisfactory analytical values have been obtained for all compounds whose empirical formulae are given.

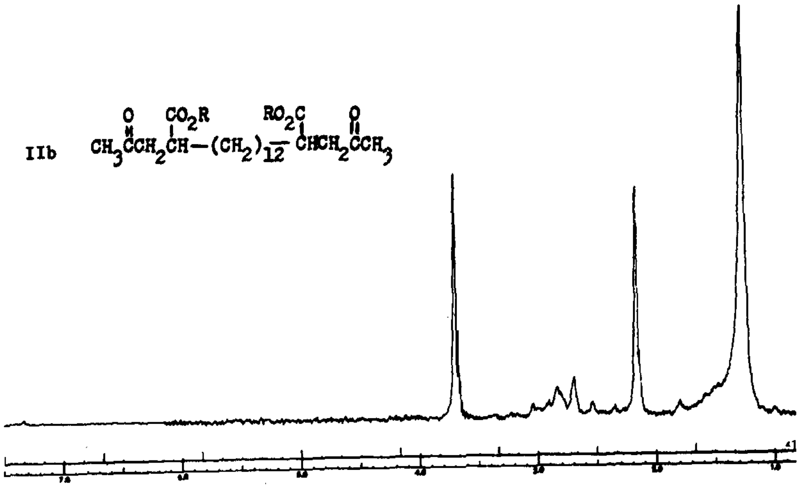
of ancepsenolide produced a diketo diacid IIa ($C_{22}H_{38}O_4$; m.p., 115-135°; bis 2,4-DNP derivative, m.p. 210-214°) which had not lost any carbon atoms. Ancepsenolide itself does not form a 2,4-DNP derivative when treated with Shine's reagent nor was I hydrolyzed under aqueous acidic conditions. These facts are all indicative of a $\Delta^{\alpha,\beta}$-butenolide grouping (5). The very strong and rather sharp absorption in the carbonyl region of the infrared spectrum of I coupled with the high extinction coefficient in the ultra-violet spectrum indicated the presence of two similarly substituted $\Delta^{\alpha,\beta}$-butenolide moieties.

Nuclear magnetic resonance spectroscopy provided further confirmation of the $\Delta^{\alpha,\beta}$-butenolide structure and gave an indication of the nature of the substitution pattern on the lactone rings of ancepsenolide. The n.m.r. spectrum (6) of I (see Fig. 1-I) revealed the presence of two vinylic protons which appeared as a multiplet of closely spaced lines centered at 7.05 δ. The position of absorption of these protons is more consistent with a proton *beta* to the carbonyl group of a $\Delta^{\alpha,\beta}$-butenolide than with an *alpha*-hydrogen on such a ring [cf. $\Delta^{\alpha,\beta}$-butenolide itself, α - H = 6.16 δ, β - H - 7.70 δ (7)]. The lack of any significant difference in chemical shift between the two vinyl hydrogens in ancepsenolide indicates that only one type of vinyl hydrogen is present in the molecule since the difference in chemical shift for α- and β-hydrogens is known to be quite large in other butenolides (cf. $\Delta^{\alpha,\beta}$-butenolide above).

This suggested that the proton resonance at 7.05 δ is due to the combined signals from two butenolide rings each having one vinyl hydrogen. The area under the multiplet at 5.07 δ also corresponds to two protons and the chemical shift of this band is consistent with that expected for a proton on the γ-carbon of a $\Delta^{\alpha,\beta}$-butenolide ring (cf. β-angelica lactone, γ - H - 5.2 δ). Furthermore it may be noted that the two peaks (6 protons) centered at 1.40 δ resemble the doublet arising from the methyl resonance

FIG. 1





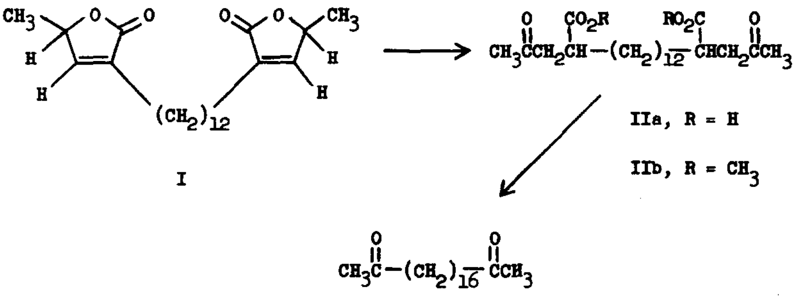
IIb $\mathrm{CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{CO_2R}{\overset{|}{C}H}-(CH_2)_{12}-\overset{RO_2C}{\overset{|}{C}H}CH_2\overset{O}{\overset{\|}{C}}CH_3}$

in β-angelica lactone in chemical shift and coupling constant. Thus the proton signals centered at 7.05, 5.07, and 1.40 δ are all consistent with the interpretation that there are two identical butenolide rings in ancepsenolide. The details of these splitting patterns will be discussed below.

Hydrogenation (Pt/ethyl acetate) of I afforded two isomeric tetrahydro derivatives, $C_{22}H_{38}O_4$, m.p. 135.5-136.6° and 105-106°, whose infrared spectra exhibited intense, sharp bands at 1758 cm^{-1} (5 membered lactone). The n.m.r. spectra of the isomeric tetrahydroancepsenolides were identical and displayed chemical shifts in agreement with those found for γ-valerolactone.

Esterification of the diketo diacid IIa with methanol (or diazomethane) produced a mixture of diketo diesters ($C_{24}H_{42}O_4$) from which samples having various melting point ranges within the limits of 48-84° were isolated by fractional crystallization. The infrared spectra of various of these samples each showed carbonyl absorption at 1730 cm^{-1} (ester) and 1712 cm^{-1} (ketone). A bis 2,4-DNP derivative of the mixture of diketo diesters exhibited carbonyl absorption only at 1735 cm^{-1} (ester).

The n.m.r. spectrum of the diketo diesters (Fig. 1-IIb) revealed the presence of two methyl ketones, 2.16 δ, two methyl ester groups, 3.68 δ, 24 methylene hydrogens, 1.25 δ, and six other hydrogens in the region 2.25-3.2 δ. On the basis of this spectrum it was possible to assign a tentative structure, IIb, for the diketo diester and hence for ancepsenolide, I, which incorporates the features suggested by the chemistry and the spectra of the foregoing compounds.



I

IIa, R = H

IIb, R = CH_3

$$CH_3\overset{O}{\overset{\|}{C}}CH_2\underset{}{\overset{CO_2R}{CH}}-(CH_2)_{12}-\overset{RO_2C}{CH}CH_2\overset{O}{\overset{\|}{C}}CH_3$$

$$CH_3\overset{O}{\overset{\|}{C}}-(CH_2)_{16}-\overset{O}{\overset{\|}{C}}CH_3$$

III

The placement of the central methylene chain on the α,α′-carbons of ancepsenolide follows from the assignment of the vinyl hydrogens to the β,β′-positions on the basis of their low field resonance in the n.m.r. spectrum (see above).

The structure II also accounts for the melting point ranges observed for the diketo diacid and its ester since each would be expected to be a mixture of diastereomers.

Additional evidence for the proposed structure of ancepsenolide was obtained from the following experiments. Ozonolysis of ancepsenolide in methylene chloride at room temperature followed by treatment with hydrogen peroxide yielded tetradecane-1,14-dioic acid, m.p. 122-125° (mixed m.p. with authentic sample of m.p. 124.5-126.5° showed no depression). The dimethyl ester of the degradation acid exhibited the same retention time in v.p.c. analysis as authentic dimethyl tetradecane-1,14-dioate.

The isolation of the tetradecane-1,14-dioic acid establishes the nature of the connecting link between the two lactone rings in ancepsenolide. The point of attachment of the methylene chain to the lactone rings was confirmed in the following way. Oxidative decarboxylation (8) of the diketo diacid IIa yielded a mixture of unsaturated ketones (*cis, trans* forms of the α,β-, and β,γ-unsaturated isomers) which upon hydrogenation afforded a single product, m.p. 90.0-92.0°, that was identified as eicosane-2,19-dione, III, by its melting point [lit. 90.5°-92.0° (9)] and by n.m.r. analysis. The fact that a straight chain diketone results from removal of the carboxyl groups confirms the structure IIa since the alternative arrangement for the diketo diacid having the γ-keto acid moieties connected via the carbons *beta* to the carboxyl groups would have given rise to a branched diketone at this point.

The final evidence for the butenolide nature of ancepsenolide was obtained by the reconversion of the diketo diacid IIa, via treatment with refluxing acetic anhydride containing a trace of p-toluenesulphonic acid, to a neutral, white solid (m.p. 90.5°-92.0°, no depression on admixture with I) whose n.m.r. spectrum was identical with that of the natural product.

The multiplicity of the peaks in the n.m.r. spectrum of ancepsenolide can be accounted for by the proposed structure as follows. The band at 7.05 δ(vinyl hydrogens) which appears as a quartet (see Fig. 1-I-a′) can be interpreted as an overlapping pair of triplets which arise from coupling (J=1.5 cps) between the lactone hydrogen and the vinylic proton and a second splitting (J=1.3 cps) attributable to coupling with the two equivalent allylic hydrogens in the central methylene chain (10).

One would expect the band at 5.07 δ assigned to the hydrogen on the lactone to appear as an octet due to splitting by the methyl hydrogens and a second splitting by the adjacent vinyl hydrogen. Indeed this portion of the spectrum does reveal a basic, symmetrical quartet (J=6.8 cps) in which each peak is split again into what seems basically a doublet. However, expansion of this portion of the spectrum (Fig. 1-I-b′) reveals that the central peaks of this fundamental quartet have small but distinct shoulders which indicate more complicated splitting. The presence of the shoulders on the central pairs of peaks leads us to suggest that a long range homoallylic coupling with the α,α′-methylene groups of the connecting aliphatic chain is giving rise again to overlapping pairs of triplets which appear as poorly defined quartets. Thus the major splitting of the lactone hydrogen absorption is assigned to coupling with the methyl group (quartet, J=6.8 cps). This quartet is split by the adjacent vinyl hydrogen (J=1.6 cps) and again by a long range coupling (J=appr. 1.5 cps) with the methylene chain to produce the overlapping triplet arrangement.

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References

1. (a) Part IV, L. S. Ciereszko, D. H. Attaway, M. A. Wolf, *Petroleum Research Fund, 8th Annual Report*, 33 (1963); (b) Part I, L. S. Ciereszko, D. H. Sifford, A. J. Weinheimer, *Ann. N. Y. Acad. Sci.*, 90, 917-919 (1960).
2. To whom inquiries concerning this paper should be addressed.
3. K.W.K. Gratefully acknowledges support from a NSF Summer Research Participation Program for Teachers of College Chemistry, 1964.
4. F. M. Bayer, "The Shallow-Water Octocorallia of the West Indian Region", Martinus Mijhoff, The Hague, Netherlands, p. 272-277 (1961).
5. For a recent review of the chemistry of butenolides see Y. Shyamsunder Rao, *Chem. Rev.*, 64, 353 (1964).
6. NMR data were obtained at 60 mc in deuteriochloroform with tetramethylsilane as internal standard.
7. R. Freeman, *Mol. Physics*, 5, 499 (1962).
8. Unpublished method for oxidative decarboxylation of γ-keto acids by P. H. Washecheck, L. H. Kelly, and A. J. Weinheimer.
9. D. E. Ames and R. E. Bowman, *J. Chem. Soc.*, 1057 (1952).
10. S. Sternhell, *Rev. Pure and Appl. Chem.*, 14, 15 (1964).