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THE STRUCTURE OF ANNONALIDE

Fulvia Orsini and Francesca Pellizoni*

Centro per lo Studio delle Sostanze Organische Naturali del CNR,
Istituto di Chimica Organica della Facoltà di Scienze, Università
degli Studi di Milano, 20133 Milano, Italy

Andrew T. McPhail* and Kay D. Onan

Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706, U.S.A.

Ernest Wenkert*

Department of Chemistry, Rice University, Houston, Texas 77001, U.S.A.

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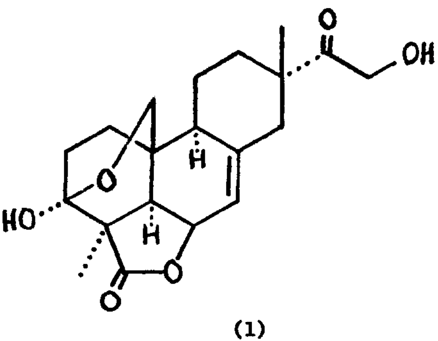
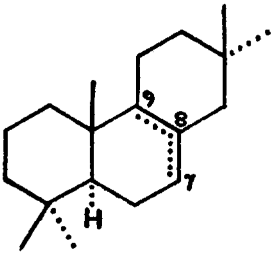
A recent study of the structure of annonalide, a diterpenoid constituent of Annona coriacea, led to the assignment of configuration (1) for the natural product.[1,2] This was based on a gross structure analysis by degradative, chemical means and spectral inspection of the compound and its degradation products[1] as well as on stereochemical analyses by comparison of the rotatory dispersion, ^{1}H NMR and mass spectral properties of the olefinic degradation product (2)[1] with those cited for the hydrocarbon in the literature,[3] by direct comparison of the isomeric hydrocarbon (3) with a sample derived from isopimaradiene[1] and by the ^{1}H and ^{13}C NMR spectral determination of the presence of an axial methyl group and equatorial vinyl function at C(13) of the degradation product (4),[2] 13-substituent orientations characteristic of pimaradienic substances.[4]

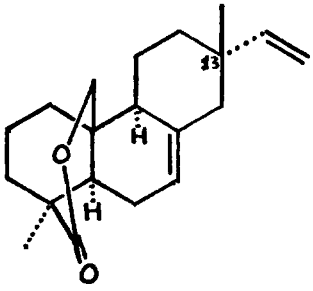


(1)



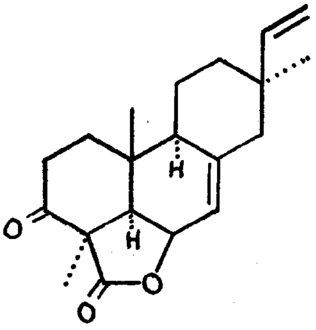
(2) $\Delta^{7,8}$, 9α-H

(3) $\Delta^{8,9}$



(4)

At the time of the publication of the annonalide structure[1,2] there appeared a description of the structures of momilactones A (5) and B (6), seed husk constituents of *Oryza sativa* L., based mostly on the x-ray analysis of lactone A.[5] Despite the extraordinary similarity of especially momilactone B (6) with annonalide (1) and the nearly identical ^{13}C chemical shifts of carbon centers proximate to C(13) in lactones (4), (5) and (6) the momilactones were assigned[5] a C(13) configuration inverted from that of annonalide. As a consequence a correlation of the latter with momilactone B was undertaken.



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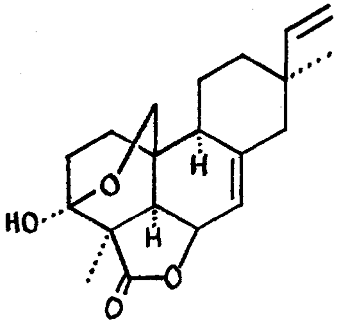

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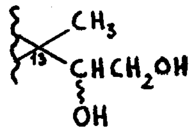
(7)



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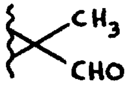

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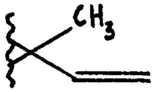
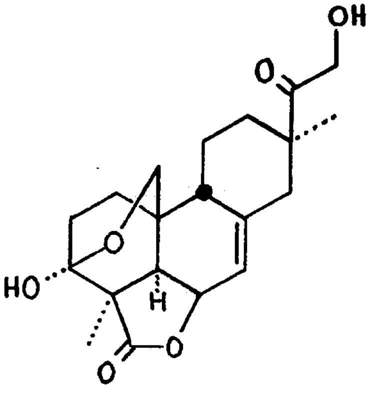
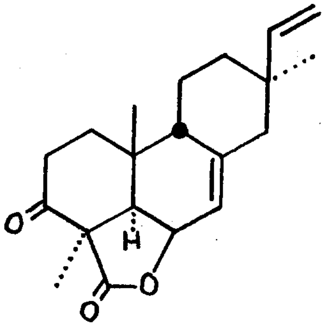


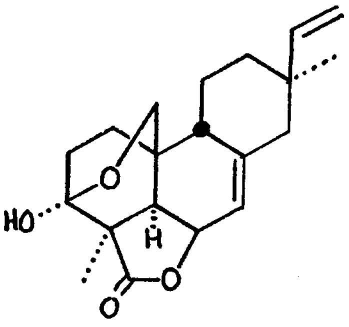
Reduction of annonalide with zinc borohydride in ether solution gave a diol stereoisomer mixture (7) [ir ($CHCl_3$) OH 3500 (s), C=O 1755 (s) cm^{-1}; m/e 364 (M$^+$)] whose oxidation with periodic acid in dioxane yielded aldehyde (8) [ir ($CHCl_3$) OH 3500 (m), aldehyde CH 2720 (m), C=O 1760 (s), 1730 (s) cm^{-1}; m/e 332 (M$^+$); ^{1}H NMR (D$_5$-pyridine) δ 9.60 (s, 1, aldehyde H)]. Treatment of the latter with methylenetriphenylphosphorane in tetrahydrofuran solution led to a crystalline lactone (9), mp, mmp 240-242°, identical in its ir, ^{1}H NMR and mass spectra with momilactone B.[6] This result is compatible with the ^{13}C NMR-based conformation of the C(13) substituents of annonalide, only if the latter is assigned the C(13) stereochemistry related to that of the momilactones and all three natural lactones possess a 9β-hydrogen configuration, i.e. the structures of annonalide, and momilactone A and B being (10), (11) and (12), respectively.



(10)



(11)



(12)

In order to remove any ambiguity concerning the structure and stereochemistry of annonalide, the compound was subjected to single-crystal x-ray analysis which confirmed the constitution to be as shown in (10). Crystals are orthorhombic, space group $\underline{P}2_12_12_1$, with $\underline{a}$ = 11.99(1), $\underline{b}$ = 22.20(1), $\underline{c}$ = 6.66(1) Å, $\underline{Z}$ = 4. Intensity data were collected on an Enraf-Nonius CAD 3 diffractometer (Ni-filtered Cu-$\underline{K}_\alpha$ radiation, λ = 1.5418 Å; θ-2θ scans). The structure was solved by direct methods by use of MULTAN;[7] atomic positional and thermal parameters (anisotropic C, O; fixed H contributions) were refined by full-matrix least-squares calculations to $\underline{R}$ = 0.056 over 638 statistically significant [$\underline{I} > 2.0\sigma(\underline{I})$] reflections.

The lactones (10), (11) and (12) are the first authentic examples of 9-epimeric, pimaradienic diterpenoid substances[8,9,10] and thus represent a violation of the heretofore assumed universality of the trans-anti ring skeletal arrangement among tri- and tetra-carbocyclic diterpenes.[11]

References

(1) P. Mussini, F. Orsini, and F. Pellizoni, J. Chem. Soc. Perkin I, 2551 (1973).

(2) P. Mussini, F. Orsini, F. Pellizoni, B. L. Buckwalter, and E. Wenkert, Tetrahedron Lett., 4849 (1973).

(3) C. R. Enzell and B. R. Thomas, Acta Chem. Scand., **19**, 1875 (1965); C. R. Enzell and S. R. Wallis, Tetrahedron Lett., 243 (1966).

(4) E. Wenkert and B. L. Buckwalter, J. Am. Chem. Soc., **94**, 4367 (1972).

(5) T. Kato, C. Kabuto, N. Sazaki, M. Tsunagawa, H. Aizawa, K. Fujita, Y. Kato, and Y. Kitahara, Tetrahedron Lett., 3861 (1973).

(6) An authentic sample of momilactone B was provided kindly by the late Professor Y. Kitahara.

(7) G. Germain, P. Main, and M. M. Woolfson, Acta Cryst., **A27**, 368 (1971).

(8) Dr. Tadahiro Kato has informed us kindly [cf. also M. Tsunakawa, A. Ohba, N. Sasaki, C. Kabuto, T. Kato, Y. Kitahara, and N. Takahashi, Chem. Lett., 1157 (1976)] that the momilactones possess a 9β-H configuration and that, although the earlier x-ray analysis established such a stereochemistry, an inadvertent error had been made in their portrayal.

(9) Naturally occurring isopimara-9(11),15-diene-3β,19-diol [P. R. Jefferies and T. Ratajczak, Aust. J. Chem., **23**, 173 (1973)] has been assumed to be derived from a 9-epimeric, pimaradienic skeleton.

(10) For a 9-epimeric, hence trans-syn sesquiterpene system see F. Bohlmann, D. Schumann, and C. Zdero, Chem. Ber., **107**, 644 (1974).

(11) A. I. Scott, F. McCapra, F. Comer, S. A. Sutherland, D. W. Young, G. A. Sim, and G. Ferguson, Tetrahedron, **20**, 1339 (1964).