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THE OCCURRENCE OF TWO NEW PROSTAGLANDIN DERIVATIVES (15-epi-PGA_2 AND ITS ACETATE, METHYL ESTER) IN THE GORGONIAN PLEXAURA HOMOMALLA[1]

CHEMISTRY OF COELENTERATES. XV.[2]

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We have previously noted the presence of terpenoid and other types of compounds in the lipid fractions of the group of marine invertebrates known as gorgonians, and now wish to report the occurrence of relatively large quantities of two prostaglandin derivatives in the gorgonian Plexaura homomalla (Esper) from the Caribbean region. These compounds, 15-epi-PGA_2 (I) and its diester (II), present in the air dried cortex to the extent of 0.2% and 1.3%, respectively, are epimeric with the potent mammalian hormone at the allylic hydroxyl center. They are devoid of the dramatic blood pressure lowering (dog) effect of PGA_2 itself.[3] Their function, like that of other compounds occurring in the gorgonians, remains speculative.

Most of the structure determination studies were performed with the diester (II), which was isolated by chromatography of the crude hexane extract in benzene/ethyl acetate on silicic acid. High resolution mass spectrometry established its composition as $C_{23}H_{34}O_5$ and demonstrated the loss of acetic acid and the even-mass fragment $C_6H_9CO_2Me$. The IR spectrum of (II) showed carbonyl absorptions at 1735 cm^{-1}, typical of simple esters, and at 1710 cm^{-1}, compatible with a conjugated cyclopentenone. The hexahydro-diester (III), formed on hydrogenation over palladium showed no hydroxyl absorption in the infrared, and carbonyl absorption only at 1735 cm^{-1}. The ultraviolet absorption maximum at 300 nm (ε=30.7) confirmed the presence of a cyclopentanone in (III). The mass spectrum of (III) showed the loss of the even-mass fragment $C_6H_{11}CO_2Me$, suggesting the presence of this side chain in the alpha position of the cyclopentanone, as well as the loss of acetic acid and the fragment C_8H_{15} suggesting the presence of an acetate-bearing side chain.

The nmr spectrum of (II) showed two sharp methyl singlets at δ 1.98 (acetate) and 3.61 (methoxyl) and a third methyl group as a perturbed triplet characteristic of an alkyl chain terminus at δ 0.89. A pair of double doublets at δ 6.12 and 7.44 (J=2, 6Hz) characterized the unsubstituted conjugated double bond (C-10,11), and their multiplicity clearly indicated a single substituent at C-12. Decoupling showed the 10 and 11 protons to be coupled to the one proton signal at δ 3.22 (H-12), which was also coupled to the 13 and 14 protons absorbing on the downfield side of the vinyl proton envelope at δ 5.2-5.7. The signal for the proton under the secondary allylic acetate also appeared in this region, and shifted from δ 5.15 to 4.80 upon formation of (III). The nature of this acetate was further confirmed by the shift of this signal to δ 3.63 on hydrolysis of (III) to the free hydroxy acid (IV), m.p. 71.5-72.5°, $[\alpha]_D^{25}$-32° (c=0.79, $CHCl_3$).

The data presented thus far is fully consistent with structure (II) for the diester but does not locate the position of the isolated double in the alpha situated side chain. Evidence for its location at C-5 followed from neutral permanganate oxidation of (II) which afforded glutaric acid shown to be identical with authentic material (as dimethyl ester) by gas chromatography. The location of the acetate function was confirmed chemically by the Baeyer-Villiger oxidation of the diketo ester obtained from Jones oxidation of the methyl ester of (IV). Saponification of the product mixture afforded 1-pentanol and hexanoic acid from the neutral and acid fractions. Each was identified by gas chromatography versus authentic compounds on three different columns.

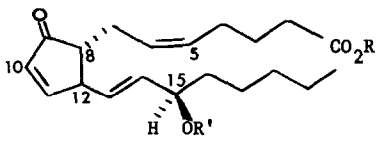
The free hydroxy acid (I), also isolated from this organism, was converted to the diester (II), and shown to be identical by ir and nmr spectra. Compound (IV) was obtained by hydrogenation of (I) and shown to be identical with that produced from the diester by rotation, ir and nmr spectroscopy, Rf in tlc, retention time in gas chromatography (as methyl esters) and m.m.p.

Though possessing the same gross structure as mammalian PGA_2, compound (I) was inactive in physiological tests, suggesting diastereomerism at one or more of the five possible sites in the molecule. I and PGA_2 display nearly identical ir spectra (thick film). A hydrogenation study, performed by interrupting the reaction at intervals and examining the partially hydrogenated mixture by both ir and nmr spectroscopy, showed preferential hydrogenation occurring at the cis double bond at position 5 (disappearance of the 1350 cm^{-1} and upfield vinyl absorptions, δ 5.41) and slower hydrogenation occurring at the trans double bond at position 13 (disappearance of the 970 cm^{-1} and downfield vinyl absorptions, δ 5.58). Similar absorptions are present in the spectra

of mammalian PGA_2, and it can be concluded that the double bond geometries of (I) are identical, i.e., cis-5 and trans-13.

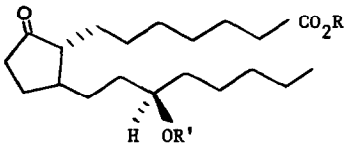
The ORD curves of mammalian PGA_2 and of (I) and (II) all show strongly positive Cotton effects, indicating identical configurations at position 12.[4] The ORD curves of mammalian PGE derivatives (saturated cyclopentanone system) are sensitive to the configuration at position 8,[5] and show negative Cotton effects, as do the saturated compounds (III) and (IV). Both the rotation and Cotton effect of (IV) were unchanged after prolonged exposure to methanolic KOH, further demonstrating the more stable trans relationship of the two side chains. Thus the absolute configurations of (I) and (II) at positions 8 and 12 are also identical with those of mammalian PGA_2.

Stereochemical difference at the only remaining site, C-15, was demonstrated by conversion of (I) with base to 15-epi-PGB_2 (V), the negative rotation and CD curve of which were enantiomeric with those of PGB_2 (VI) derived from PGA_2. Further, ozonolysis of (II) afforded, in addition to monomethyl glutarate, (+)-α-acetoxyheptanoic acid which was hydrolyzed to (-)-α-hydroxyheptanoic acid. The (R) configuration of this acid[6] conclusively established the (R) configuration at C-15 in these prostaglandins, i.e., epimeric with C-15 in PGA_2.



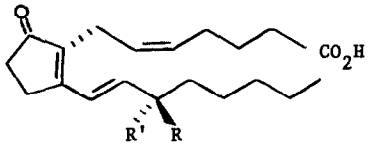
I R,R'=H

II R=Me,R'=Ac



III R=Me,R'=Ac

IV R,R'=H



V R=OH,R'=H

VI R=H,R'=OH

In the current state of limited supply of mammalian prostaglandins, the availability of large quantities of (I) and (II) from this widely distributed gorgonian invites their thorough evaluation as possible synthetic precursors to currently useful members of this important hormone system. In addition, full evaluation of their pharmacological properties may disclose utility for the 15-epi derivatives themselves.

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References

1. Presented at the "Food-Drugs from the Sea Conference", University of Rhode Island, Kingston, Rhode Island, August 24-27, 1969, and at the 158th National Meeting of the American Chemical Society, New York, New York, September 8-12, 1969.

2. Preceding paper in this series: A. J. Weinheimer and P. H. Washecheck, Tetrahedron Letters, 3315 (1969).

3. J. Nakano, submitted to J. Pharm. and Pharmacol.

4. P. W. Ramwell, J. E. Shaw, G. B. Clark, M. F. Grostic, D. G. Kaiser, and J. E. Pike, in Progress in the Chemistry of Fats and Other Lipids, 10, 256 (1968).

5. E. G. Daniels, W. C. Krueger, F. P. Kupiecki, J. E. Pike, and W. P. Schneider, J. Am. Chem. Soc., 90, 5894 (1968).

6. D. H. Nugteren, D. A. van Dorp, S. Bergstrom, M. Hamberg and B. Samuelsson, Nature, 212, 38 (1966).