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PGA_2 AND ISOMERS FROM CORAL PROSTAGLANDINS

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The availability of large quantities of 15(R)-prostaglandin compounds from a natural source,[1,2] the gorgonian Plexaura homomalla, has stimulated interest in using these compounds as precursors for producing 15(S)-prostaglandins and isomers of known biological activities[3,4]. These biological activities are associated in large part with the stereochemistry of the prostaglandins at their C-15 centers. The purpose of the present study was to utilize the major prostaglandin derived from Plexaura homomalla for conversion to prostaglandin PGA_2 (I). It was found that PGA_2 could be produced under reaction conditions which led to only minor isomerization to PGB_2 (II) and in addition prostaglandin isomers were formed via allylic rearrangement (viz. VI) that could be recycled to PGA_2.

The C-13 diastereomers resisted separation both as free hydroxy acids and as methyl esters (VI) using silicic acid and $AgNO_3$ impregnated silicic acid TLC systems. Multiple development TLC systems were used that resulted in diastereomeric mixture (VI) to appear as an elongated spot with UV visualization. The faster moving half of the spot was separated from the slower moving portion. Each was extracted from the support with ethyl acetate. On rechromatographing under the same TLC conditions these fractions appeared chromatographically identical, but NMR spectral examination (see below) showed them to be mixtures.

Treatment of the acetate, methyl diester of 15 epi-PGA_2 (III) with formic acid (0.1 molar in potassium formate) for about 60 hours at 20° gave a mixture of formate esters along with minor amounts of elimination products. The formate esters were hydrolyzed in a 95:5 mixture of methanol-1 N HCl for 16 hours yielding a mixture of methyl ester alcohols which was separated by column chromatography on silicAR CC-4 (Mallinkrodt). The methyl esters of PGA_2 (IV) and 15-epi-PGA_2 (V) were identified by comparison with authentic materials. In addition, the 13-hydroxy diastereoisomers (VI) were isolated in 32% yield uncontaminated by IV and V. A 40% yield of IV (ε_{217} = 10,800) was obtained from (III) with two recycles of reaction by-products

after a final silver nitrate chromatography. No visible impurities were detected by GLC. The initial separations of IV from the epimerization mixture was done on silicAR CC-4 (50:1). This column was reused seven times with no deactivation, and approximately 10 grams of IV was easily made in this essentially one pot transformation from the readily available prostaglandin diester (III). Reaction concs. of 1-3% by wt. of III and the corresponding formate esters were employed.

The alternative method of preparing IV by the solvolysis of an active ester (for example: mesylate) requires prior removal of the C-15 acetate. Mild methanolysis reactions of III at different conditions have been tried with only approximately 50% yield of V. Due to the importance of intermediate IV and the availability of its precursor (III) this otherwise undistinguished 40% conversion of III to IV deserves consideration as a useful method for the partial synthesis of prostaglandins from their 15(R)-diastereoisomers of coral.

The epimerization of prostaglandins at the C-15 center in formic acid under similar conditions has been reported for E and F prostaglandin isomers[5]. In these cases, however, no allylic rearrangements were reported. Probably the 13-hydroxyl isomers were formed in low yields but not characterized since the major interest of the authors seemed to be in simple epimerization of the C-15 diastereomers[5].

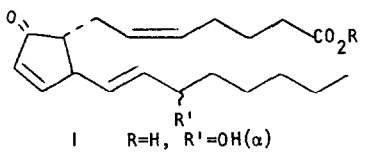
The NMR spectrum of VI can be used to distinguish between the two diastereomeric C-13 alcohols. The chemical shift for their C-11 (two doublets) signal is different, one occurring at approximately δ7.75 (J = 2,4) and the other at approximately δ7.83 (J = 2,4). Comparing the NMR of VI with that of the methyl ester of PGA_2, the doubly allylic (C-12) methine signal of PGA_2 at δ3.2(m) is noticeably absent in the spectrum of VI.

The mass spectrum of VI shows a parent ion at m/e 348 (10% of base) with fragment-peaks at m/e 330 (M-18, 13% of base) and m/e 190 (M-18-140, 57% of base) characteristic of PGA_2 derivatives[6]. The latter represents a McLafferty cleavage of the entire carboxyl side chain and loss of water from the alkyl side chain. Additional peaks at m/e 221 (71% of base) and m/e 127 (31% of base) are both consistent with cleavage of the alkyl side chain at C-12. This is not a favorable cleavage for PGA_2 ester derivatives probably due to the carbon-carbon double bond at C-13. However, cleavage for the 12, 13 carbon-carbon bond is extensive in the mass spectrum of the methyl, acetate diester of hexahydro-15 epi-PGA_2 (VII, 40% of base) in which this double bond is no longer present[7].

The IR spectrum of VI (film) showed carbonyl absorption at 1740 cm^{-1} for the methyl ester and 1710 cm^{-1} for the cyclopentenone system. Characteristic hydroxyl absorption at 3450 cm^{-1} and trans olefin at 970 cm^{-1} were also present.

Like PGA_2 VI showed a UV maximum at 217_{nm}, but the 13-hydroxyl compounds showed no observable tendency toward base isomerization to PGB type compounds until after elimination of water from the C_8 alkyl side chain.

When VI is reacted with formic acid and potassium formate under the same conditions as III, a new mixture of formate esters is obtained. After acid hydrolysis of the formate esters, the methyl esters of PGA_2, 15-epi-PGA_2 and VI were identified by TLC and isolated by column chromatography.

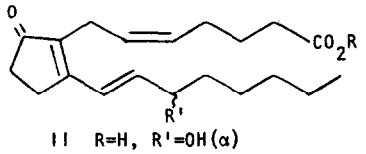


I R=H, R'=OH(α)

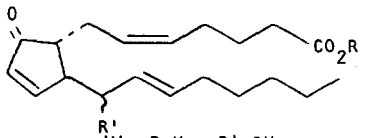
III R=Me, R'=OAc(β)

IV R=Me, R'=OH(α)

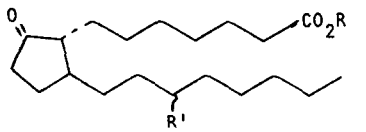
V R=Me, R'=OH(β)



II R=H, R'=OH(α)



VI R=Me, R'=OH



VII R=Me, R'=OAc(β)

Upon acid hydrolysis of VI in a 2:1 mixture of 1 N HCl-t-butyl alcohol the free hydroxyl acids VIII were obtained (M^+ 334).

Bioassay of 15 epi-PGA_2 (potency = 0.0042 compared to PGA_2) on rat uterus revealed it was virtually inactive. The methyl ester of PGA_2 (IV) was found to have only 1.5% of the activity of PGA_2 itself on rat uterus. Testing the "A" prostaglandins on rat blood pressure, showed IV to have virtually the same depressor activity as PGA_2. Both 15 epi-PGA_2 and the 13-ol diastereomeric methyl esters formed by allylic rearrangement of PGA_2 were found to have slight pressor activity[8].

References

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