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PROSTAGLANDINS AND CONGENERS IV.[1] THE SYNTHESIS OF CERTAIN 11-SUBSTITUTED DERIVATIVES OF 11-DEOXYPROSTAGLANDIN E_2 AND $F_{2\alpha}$ FROM 15-O-ACETYLPROSTAGLANDIN A_2 METHYL ESTER

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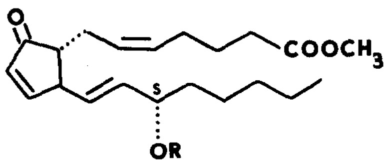
The ready availability of 15-O-acetylprostaglandin A_2 methyl ester (I) from the sea coral Plexaura homomalla (Esper)[2] makes this substance an attractive starting point for congener synthesis. In this paper we wish to report the preparation of a variety of 11-substituted-11-deoxyprostaglandins of the E_2 and $F_{2\alpha}$ series by base-catalyzed conjugate 1,4-addition to the Δ^{10}-9-keto system of I or the corresponding 15-ol II.

Diester I was obtained from the cortex of P. homomalla, gathered in Puerto Rican waters and supplied to us by the late Dr. Paul Burkholder of the College of the Virgin Islands. The 15-S configuration of I was established by ozonolysis followed by chromic acid oxidation to furnish α-acetoxyheptanoic acid, which was shown to be opposite in configuration to authentic D(+) α-acetoxypropanoic acid[3] (R-configuration) by ORD and CD comparisons.

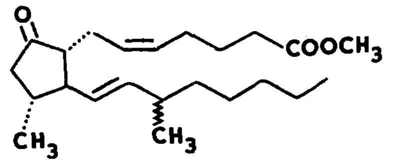
Heating I with excess thiolacetic acid afforded a 90% yield of the 11α-acetylthio derivative X [4,5] (λ max:1700 cm^{-1},$CH_3\overset{O}{\overset{\|}{C}}S$; pmr:2.3 s, 3H, $\underline{CH_3}\overset{O}{\overset{\|}{C}}S$). Carbonate-catalyzed addition of methanethiol in methanol to I rapidly provided XI, acetate hydrolysis of which was accomplished in methanol (15 ml/gm) containing a large excess of methanethiol (4 ml/gm) and sodium carbonate (2 equiv., 14 days, 25°) producing the 15-hydroxy ester XII. Michael addition of nitromethane (1 ml/gm, THF, Triton B, 1 hour) to I followed by saponification gave IV (λ max: 1550 cm^{-1}), and similar treatment with diethyl malonate afforded V [pmr: 3.6 s, 1H, $\underline{CH}(CO_2Et)_2$] in 60% and 80% yield, respectively.

Treatment of I with lithium dimethylcuprate (2 equiv., Et_2O, -20°, 15 min) followed by column chromatagraphy gave 28% of VI (pmr: 1.04 d, 3H, $\underline{CH_3}$) and 55% of 11,15-dimethyl ester III. (Displacement of allylic acetoxy groups by this reagent has been reported.[6]) In order to avoid displacement at C-15 we required PGA_2 methyl ester (II), which however is not directly available by hydrolysis of diester I, since I undergoes facile elimination of the elements of acetic acid to



I R=Ac

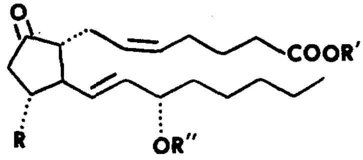
II R=H



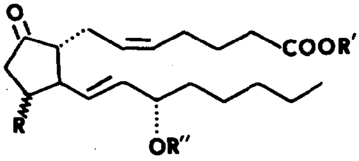
III

pmr: δ0.9 (t,3H,J=7Hz,CH_3)
0.98 (d,3H,J=7Hz,CH_3)
1.07 (d,3H,J=7Hz,CH_3)

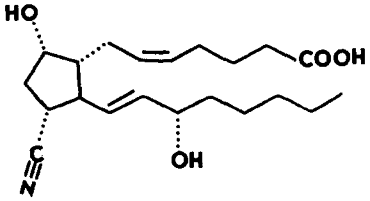
m/e: 362m$^+$(5.3%)
222(18.8%) m$^+$-$C_8H_{12}O_2$
123(100%) m/e222-C_7H_{15}
m* for 222→123 calc 68.1
obs 68.2



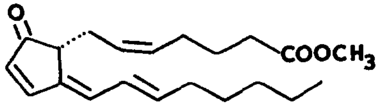
IV R=CH_2NO_2, R'=R"=H
V R=$CH(CO_2Et)_2$, R'=CH_3, R"=Ac
VI R=CH_3, R'=CH_3, R"=Ac
VII R=CH_3, R'=R"=H
VIII R=$CH=CH_2$, R'=R"=H
IX R=H R'=R"=H



X R=$S\overset{O}{\overset{\|}{C}}CH_3$,R'=$CH_3$, R"=Ac
XI R=SCH_3, R'=CH_3, R"=Ac
XII R=SCH_3, R'=CH_3, R"=H
XIII R=CN, R'=CH_3, R"=Ac
XIV R=CN, R'=R"=H
XV R=$CONH_2$,R'=CH_3, R"=Ac
XVI R=$CONH_2$,R'=R"=H
XVII R=COOH, R'=R"=H



XVIII



XIX

λ_{max}^{EtOH}: 325nm (ε=4.2)
pmr: δ7.6 (d,J=6Hz,H_{11})
6.1 (d,J=6Hz,H_{10})

form tetraenone XIX even when treated with bases such as piperidine and sodium carbonate. PGA_2 ester II was obtained indirectly by elimination[7] of methanethiol from 11α-methylthio-15-hydroxy ester XII on treatment (reflux, 4 hrs) with iodomethane (2 ml/gm) in a methanol, THF, 5% $NaHCO_3$ solution (2:5:5 ml/gm). The overall yield of II from I was 80%. Reaction of II with lithium dimethylcuprate (2.2 equiv., Et_2O, -20°, 45 min) or with the lithium divinylcuprate tributyl phosphine complex (2.2 equiv., THF, -78°, 45 min) furnished, after saponification, the 11α-methyl and 11α-vinyl derivatives of 11-deoxy PGE_2, VII (70%, m.p. 65°, pmr: 1.09 d, 3H, J=7Hz, CH_3) and VIII(70%, pmr: 5.6 m, 1H, $CH_2=\underline{CH}-$, 4.9-5.1 m, 2H, $\underline{CH_2}=CH-$), respectively.

The 11-cyano diester XIII (λ max: 2230 cm^{-1}) was prepared in high yield by treatment of I with excess acetone cyanohydrin.[8] PMR studies with XIII using $Eu(fod)_3$ indicated an epimeric mixture at C_{11} as evidenced by two acetate signals. Saponification of XIII was accomplished by treatment (96 hrs) with saturated aqueous sodium cyanide (4 ml/gm) in methanol (12 ml/gm) affording the acid XIV as a mixture[5] of C_{11} epimers. The nitrile diester XIII upon alkaline hydrogen peroxide oxidation (30% H_2O_2, 1.2 ml/gm) in a two-phase system consisting of ethanol, THF and cyclohexene (1:1:1, 6 ml/gm, reflux, 24 hrs) was converted in 30% yield to the amide diester XV obtained as a mixture (1:1) of 11α and 11β epimers (pmr: 203 Hz(s) and 205 Hz(s), $\underline{CH_3}CO_2$). Saponification of XV provided XVI, which was further hydrolysed (5 equiv. KOH, 80°, 2 hrs) to the diacid XVII.

11-Deoxyprostaglandin E_2[9] (IX) was obtained by conjugate reduction of diester I with sodium cyanoborohydride[10] followed by Jones oxidation and saponification (40% yield plus 30% recovered I). Hydrogenation of VII (5% rhodium-on-carbon, ethyl acetate, 50 psi) produced 11α-methyl-11-deoxy-13-dihydroprostaglandin E_1.

Treatment of compounds IV, VII, VIII, XI and XV with lithium perhydro-9b-boraphenalyl hydride[11] (XX), followed by saponification where necessary, provided the corresponding 11α-substituted-11-deoxy $PGF_{2\alpha}$ derivatives in good yield. The reduction of 11α/β-cyano diester XIII with XX followed by saponification afforded a mixture of four products from which there was isolated (4:1 ratio) 11-deoxy-11α-cyano $PGF_{2\alpha}$ (XVIII, the least polar, pmr: δ2.6-2.8 m, 2H, $H_{11\beta}$ and H_{12}; 4.2 m, 2H, $H_{9\beta}$ and H_{15}; 5.6 m, 3H, $H_{5,6,13}$; 5.8 dd, J∿5Hz, J∿15Hz, H_{14}) and 11-deoxy-11β-cyano $PGF_{2\beta}$ (m.p. 76-78°, the most polar, pmr: δ2.98 q, 1H, J∿7Hz, $H_{11\alpha}$; 3.96 q, 1H, J∿6Hz, $H_{9\alpha}$; 4.17, 1H, H_{15}; 5.48 m, 2H, $H_{5,6}$; 5.70 m, 2H, $H_{13,14}$). N.O.E.[12] performed upon XVIII indicated a 10% enhancement of H_{14} when H_{11} was irradiated; no such enhancement was observed for the other isomer.

The assignment of configuration to the various 11-substituents presents a problem as yet not fully resolved in each instance. Inasmuch as the 11-methylthio derivatives XI and XII were prepared under equilibrating conditions, we feel that the assignment of the trans (alpha) configuration to the major isomer is reasonably based. The nitromethyl, methyl and vinyl products appear to be epimerically pure but they were not formed under equilibrating conditions. We have intuitively assigned the α-configuration to these substituents on the basis that the approach from the less-hindered side is the more likely. However, we cannot rule out an assisted approach from the β-side, particularly with lithium dimethylcuprate.

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4. All new compounds gave consistent elemental analyses, absorbtion and mass spectra, and showed one spot on TLC unless otherwise noted (ref. 5). PMR spectra were recorded on a Varian HA-100 nmr spectrometer in $CDCl_3$ using TMS as an internal reference. In general, compounds were purified by dry column chromatography on acid-washed silica gel. Analytical samples were obtained by preparative TLC.

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