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PROSTAGLANDINS I - TOTAL SYNTHESIS OF 9β,15ξ - DIHYDROXYPROST-13-ENOIC ACID

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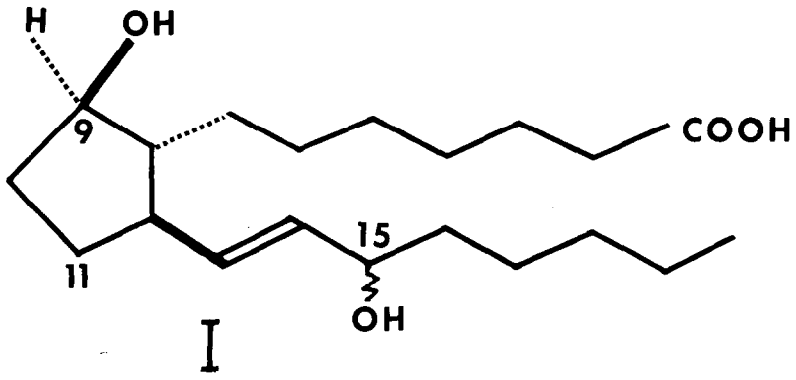
The discovery of prostaglandins - a group of biologically important compounds having diverse pharmacological properties - present in the human seminal fluid and in vesicular gland of sheep, dates back to 1933[1]. In recent years chemical investigation by Swedish workers clarified[2] the structures of several representatives of this group.

We wish to report now, the total synthesis of Compound I, which we have prepared as a mixture of two alcohols epimeric at the carbon 15. The

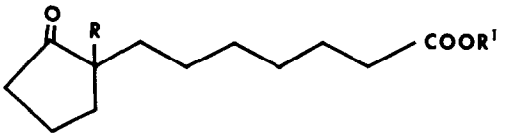


I

remaining asymmetric centres are assumed to have the configuration shown, by the mode of its synthesis and by analogy with similar cases.

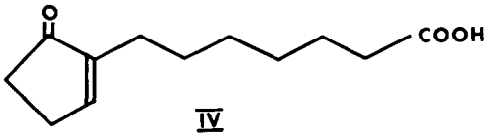
Compound I is the first pharmacologically active, totally synthetic derivative of prostanoic acid[3]. It is remarkable that it exhibits hypotensive activity[4] in spite of the lack of oxygen function at Carbon 11.

Potassium salt of ethyl 2-cyclopentanone carboxylate[5] was condensed with ω-bromoethylheptanoate[6] in dry toluene to yield the diester II ($C_{17}H_{28}O_5$, b.p. 146-8°/0.08mm, n_D^{22} 1.4557, ν max. 1740, 1718 cm^{-1}). Treatment of diester II with boiling 10% sulfuric acid for 16 hours gave acid III ($C_{12}H_{20}O_3$, eq. wt.[7] 218, n_D^{22} 1.4680; ν max. 1725, 1710 cm^{-1}, n.m.r. 10.04δ acid proton, 2,4-dinitrophenylhydrazone of the ethyl ester, $C_{20}H_{28}O_6N_4$, m.p. 74-6°). Bromination of diester II with one mole of bromine resulted in a monobromo derivative. When the latter compound was refluxed with 20% sulfuric acid in ethanol for 16-18 hours and the crude product was chromatographed, cyclopentenone IV was isolated $C_{12}H_{18}O_3$, eq. wt. 209.4, ν max. 1695, 1626, 1000 cm^{-1}, λmax. 228(4.00)[8], n.m.r. 7.28δ[9] 1 H, poorly resolved triplet; methyl ester, ν max. 1730, 1695, 1630, 1000 cm^{-1}). Cyclopentenone IV was transformed into nitrile V by the action of acetone cyanhydrin in the presence of sodium carbonate in aqueous methanol[10]. The nitrile was characterized by the disappearance of the vinyl proton in the n.m.r., of the ultraviolet spectrum and by the presence of bands at 2248, 1750 and 1705 cm^{-1} in its infrared spectrum (methyl ester, ν max. 2248, 1737 cm^{-1}). The hydrolysis of the crude keto nitrile V was achieved by refluxing with aqueous 8% sodium hydroxide for four hours to yield diacid VI ($C_{13}H_{20}O_5$, eq. wt. 127.5, m.p. 73-74.5°, ν max. broad acid hydroxyl, 1737, 1705 cm^{-1}, n.m.r. of dimethyl ester 3.62δ and 3.72δ 3 H each, of ester methoxyl). The diacid VI, on treatment with methanol containing 1.5 mole of p-toluenesulfonic acid per mole of diacid at 25° for 55 minutes gave the monoester VII ($C_{14}H_{22}O_5$, eq. wt. 278, m.p. 58-60°, ν max. 1732, 1705 cm^{-1}, n.m.r. 3.71δ 3 H - OCH_3 of ester, 10.01δ acid proton). The

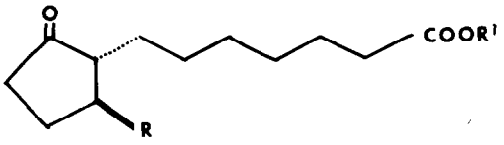


II R=$COOC_2H_5$, R =-C_2H_5

III R=R^1=H



IV



V R=CN , R^1=H

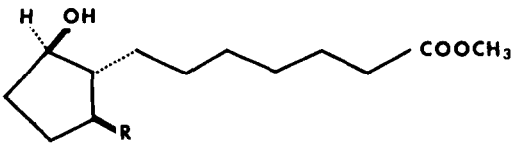
VI R=COOH , R^1=H

VII R=COOH , R^1=CH_3

VIII R=COCl , R^1=CH_3

IX R=CO-CH=CHCl , R^1=CH_3

X R=CO-CH_2-$CH(OCH_3)_2$, R^1=CH_3



XI R= CHOH-CH_2-$CH(OCH_3)_2$

XII R= CH=CH-CHO

XIII R=CH=CH-CH-$(CH_2)_4$-CH_3
OH

monoester VII was converted to its acid chloride VIII (max. 1785, 1737 cm^{-1}), which on treatment with acetylene in presence of aluminum chloride in carbon tetrachloride yielded a crude product from which chlorovinyl ketone IX [11] was isolated after chromatography ($C_{16}H_{23}O_4Cl$, ν max. 1727, 1685, 1585, 940 cm^{-1}, λmax. 234mμ(4.08), n.m.r. 6.6δ 1 H doublet, 7.42δ 1 H doublet J=14 c.p.s. vinyl protons, 3.65δ 3 H - OCH_3 of ester). The chlorovinyl ketone IX was converted to acetal X ($C_{18}H_{30}O_6$, ν max. 1733, 1718 cm^{-1}, n.m.r., 3.60δ, 3.48δ, 3.33δ 3 H each ester - OCH_3, 4.72δ carbinolic proton) with methanolic sodium hydroxide. Reduction of the diketone X with sodium borohydride yielded a mixture of stereoisomers of alcohols XI. This crude mixture when treated with 2N sulfuric acid was transformed to a mixture of two epimeric aldehydes from which the predominant isomer XII - assumed to have the stereochemistry shown, was isolated ($C_{16}H_{26}O_4$, ν max. 3600, 3400, 2745, 1726, 1680, 1630, 975, λmax. 228mμ (3.85) n.m.r. 3.68δ 3 H - OCH_3 of ester, 4.2δ 1 H carbinolic, doublets centred at 6.25δ and 6.8δ 2 H vinylic J=8 c.p.s. doublet at 9.6δ 1 H aldehydic proton J=4 c.p.s.).

Treatment of aldehyde XII with pentyl magnesium bromide in dry ether, gave after chromatography of the crude product the methyl ester XIII ($C_{21}H_{38}O_4$, ν max. 3600, 3430, 1730, 1625, 978, n.m.r. 3.65δ 3 H - OCH_3 of ester, 5.45δ 2 H vinyl, 3.95δ and 3.35δ 2 H carbinolic). Compound I was obtained by alkaline hydrolysis in the usual manner.

The mass spectral analysis of the methyl ester XIII revealed the typical fragmentation pattern observed in the spectra of natural prostaglandins[12]. The m/e value of some of the typical fragments are listed in Table I.

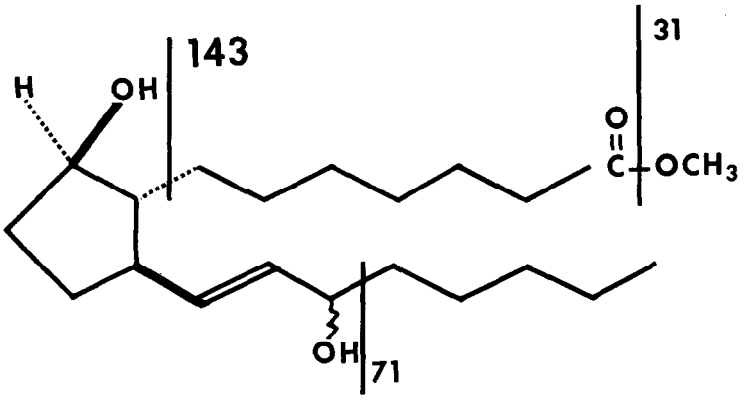


TABLE I

		PGE_1^3	METHYL ESTER OF COMPOUND I
(1)	M	(368)	(354)
(2)	M-18	350	336
(3)	M-2x18	332	318
(2)	- 31	319	305
(3)	- 31	301	287
(2)	- 71	276	265
(3)	- 71	261	247
(2)	- 143		193
(3)	- 143		175

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3. For details on nomenclature see footnote 2, in Ann. Rev. Biochem. 34, 101(1965).

4. The compound was assayed in anaesthetized cats recording the fall in arterial blood pressure. Details of these experiments as well as the other aspects of the pharmacology of the compound will be published elsewhere (Dr. G. Beaulieu et al).

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7. Equivalent weights were determined by titration with 0.01N NaOH. Infrareds were all done in chloroform, ultraviolet spectra were recorded in 95% ethanol, N.M.R. were recorded on 60 Mc Varian Spectrometer and mass spectra were done on Hitachi RMU-6D.

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