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THE SYNTHESIS OF 6,7-DIDEHYDRO-5-HYDROXY AND 4,5-DIDEHYDRO-6-HYDROXYPROSTAGLANDIN $F_{1\alpha}$: PHOTOSENSITIZED OXYGENATION OF PROSTAGLANDIN $F_{2\alpha}$ [1)]

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Photosensitized oxygenation of prostaglandin $F_{2\alpha}$ methyl ester was studied to prepare 6,7-didehydro-5-hydroxy and 4,5-didehydro-6-hydroxyprostaglandin $F_{1\alpha}$ methyl ester. 6,7-Didehydro-5β-hydroxyprostaglandin $F_{1\alpha}$ is interesting from the viewpoints of structure-activity relationships, because the two side chains of it have the symmetrical allylic alcohol structure.

It has been suggested that some receptors for prostaglandins may have a two-fold rotational(diad) axis of symmetry, so that the oxygen binding sites may occur in symmetrical pairs.[2)] According to this hypothesis, prostaglandin derivatives in which the two side chains possess allylic alcohol structure with the same absolute configuration, are interesting from the viewpoints of the structure-activity relationships. We wish to describe herein the preparation of 6,7-didehydro-5-hydroxy and 4,5-didehydro-6-hydroxyprostaglandin $F_{1\alpha}$ (7a, 7b, 8a, and 8b) which are expected to show specific biological activities due to the partial symmetrical structure in the molecule.

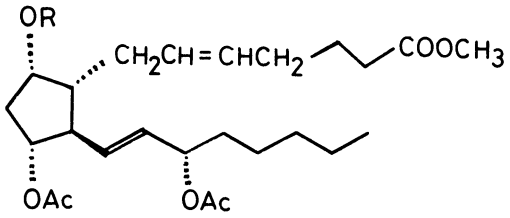
A solution of 9,11,15-tri-O-acetylprostaglandin $F_{2\alpha}$ methyl ester 1 and rose bengal(0,01~0.03 mol eq.per 1) in methanol was irradiated externally with a high-pressure mercury vapor lamp(Toshiba HO400-PL/4, 400W) in an ice-water cooled (4 ~ 10 °C) apparatus through which oxygen was continuously bubbled (ca.300 ml/min).[3)] The oxygen was simply vented after passage through the solution and the reaction was monitored by thin layer chromatography examination of aliquots.[4)] Hydroperoxides thus obtained were immediately reduced by the

addition of the solution of potassium iodide in acetic acid-methanol (weight ratio = 1:2:7) to give a mixture of allyl alcohols (85%). The mixture was separated by repeated silica gel column chromatography (cyclohexane-ethyl acetate 1:1 as eluent) to afford the four isomers (3a, 3b, 4a, and 4b).[6] These isomers were hydrolyzed with potassium carbonate in methanol-H_2O to give corresponding carboxylic acids (7a, 7b, 8a, and 8b), respectively. Less polar isomers (7a and 8a) were tentatively assigned the α-configuration from the consideration about the polarity and the conformation of the molecule.

Diacetate 2 was prepared by 6,9-epoxycyclization of prostaglandin $F_{2\alpha}$ methy ester with N-bromosuccinimide,[7] followed by 11,15-di-O-acetylation with acetic anhydride-pyridine, and by reductive ring opening with zinc-acetic acid (total yield, 75%). Reductive ring opening of 11,15-di-O-acetyl-5-bromo-6,9-epoxide (11,15-di-O-acetyl-5-bromo PGI_1 methyl ester) afforded the mixture of 5(Z)- and 5(E)-diacetate (2, Z/E = 1). The diacetate 2 was similarly oxygenated by irradiation, followed by reduction to give a mixture of allyl alcohols (5a, 5b, 6a, and 6b). The mixture can easily be separated by silica gel column chromatography into two regioisomers 5a+5b (35%) and 6a+6b (34%).[8] The diacetate 2 is preferable to the triacetate 1 for the separation of 5- and 6-hydroxy regioisomers.

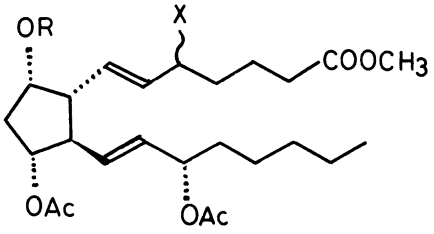
To clarify the structure, the mixture of 5a and 5b and that of 6a and 6b were converted to corresponding enones 11 and 12 with active manganese dioxide,[9] respectively. The structure of 11 and 12 was established on the basis of the NMR spectra.[10][11]

Bioassay of 6,7-didehydro-5β-hydroxyprostaglandin $F_{1\alpha}$ (7b) on the contraction of isolated fundus muscle(hamster) exhibited about 1.7% activity of prostaglandin $F_{2\alpha}$.[12]



1 R = Ac

2 R = H

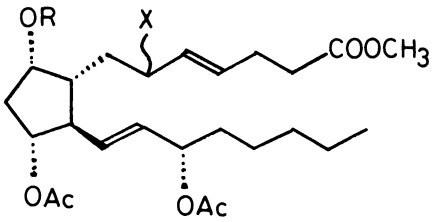


3a X = α-OH R = Ac

3b X = β-OH R = Ac

5a X = α-OH R = H

5b X = β-OH R = H

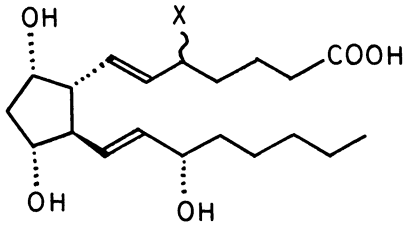


4a X = α-OH R = Ac

4b X = β-OH R = Ac

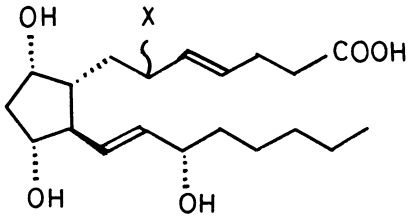
6a X = α-OH R = H

6b X = β-OH R = H



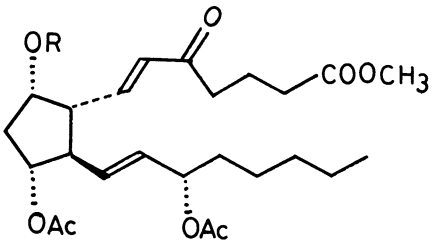
7a X = α-OH

7b X = β-OH



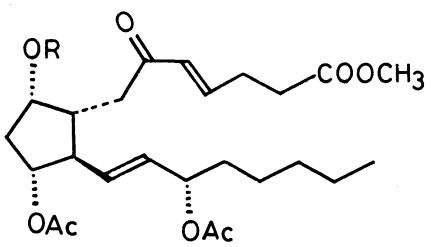
8a X = α-OH

8b X = β-OH



9 R = Ac

11 R = H



10 R = Ac

12 R = H

References and Notes

1) Synthesis of prostaglandins and their congeners Part V. see Part IV, K.Ohno and M.Naruto, Tetrahedron Letters, submitted for publication.

2) C.R.Beddell and P.J.Goodford, Prostaglandin, 13, 493(1977).

3) R.W.Denny and A.Nickon, Organic Reactions, Vol 20, 2, 133(1973) John Wiely & Sons, Inc..

4) TLC(silica gel; Merck TLC plate, Art 5715, cyclohexane-ethyl acetate 1:2 as eluent), 1: Rf = 0.62, four isomers of hydroperoxides: Rf = 0.50~0.55, allyl alcohols: Rf = 0.44.

5) The use of another reducing reagents such as sodium sulfite or sodium thiosulfate gave only poor results.

6) The four isomers(3a,3b,4a, and 4b); triacetate 4a as the first eluted fraction, 3a as the second one, 4b as the third one, and 3b as the last one.

7) a) E.J.Corey, C.E.Keck, I.Szekely, J.Am.Chem.Soc., 99, 2006(1977).
b) K.Ohno, H.Nishiyama, N.Naruse, S.Nishio, and M.Morita, Japan Kokai, 53-127460.

8) TLC(silica gel, cyclohexane-ethyl acetate 1:1 as eluent), 2: Rf = 0.8, four isomers of hydroperoxides: Rf = 0.65~0.75, 5a+5b: Rf = 0.2, 6a+6b: Rf = 0.35.

9) L.Crombie and J.Crossley, J.Chem.Soc.,4983(1963).

10) 11: 39%, NMR;($CDCl_3$,δ ppm), 6.10(d,1H,J=18 Hz, $C_{(6)}H$), 6.90(dd,J=18 Hz,7 Hz, $C_{(7)}H$), IR;(ν cm^{-1}), 1740,1680,1630. 12: 81%, NMR;($CDCl_3$,δ ppm),6.10 (d,1H,J=18 Hz, $C_{(5)}H$), 6.86(dt,1H,J=18 Hz,7 Hz, $C_{(4)}H$), IR;(ν cm^{-1}),1740, 1665,1620.

11) Oxidation of triacetate 3b and 4b with active manganese dioxide; 9: 92%, NMR($CDCl_3$,δ ppm),6.09(d,1H,J=18 Hz), 6.70(dd,1H,J=18 Hz,7 Hz), 10:91%, NMR($CDCl_3$,δ ppm),6.08(d,1H,J=18 Hz), 6.80(m,1H), respectively.

12) Biological activity was measured by Dr. Morita and Mr. S.Nishio in our laboratory. Full bioassay details will be reported elsewhere.

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