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SYNTHESIS OF 6,7-DEHYDRO-5-OXO-PROSTAGLANDIN I_1: A STABLE ANALOG OF PROSTACYCLIN[1)]

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Abstract; Stable analogs of prostacyclin, 6,7-dehydro-5-oxo-prostaglandin I_1 and derivatives, were synthesized from readily available 6,7-dehydro-5-hydroxy-prostaglandin $F_{1\alpha}$ methyl ester[2)].

Comprehensive search of both the synthesis and the biological activity of prostacyclin 1 and its analogs has been reported in recent literatures to show potent activities such as inhibition of blood platelet aggrgation, vasodilation, gastric acid secretion, and so on.[3)] Synthetic analogs were evaluated not only for the improvement of chemical instability of natural prostacyclin due to enol ether linkage but also of its diversity of physiological activities as potent therapeutic agents. We wish to describe herein the synthesis of 6,7-dehydro-5-oxo-prostaglandin I_1, in which enol ether linkage is stabilized through the conjugation of enone-form, from easily available 6,7-dehydro-5-hydroxy-$PGF_{1\alpha}$ derivative 3[2)].

Reaction of 11,15-di-O-acetyl-6,7-dehydro-5-hydroxy-prostaglandin $F_{1\alpha}$ methyl ester 3 in tetrachloromethane (15mL/g of 3) with 1.1 equiv. of N-bromo-succinimide at ambient temperature for 4 hr afforded the diasteremeric 5-hydroxy bromo ether 4 (27%) and 5 (33%)(observed Rf values on silica gel TLC plates with ethyl acetate-cyclohexane 4:5 as eluent, 0.3 for 4 and 0.5 for 5).[4)] Stereochemistry of 4 (endo-hydrogen at C_6 and exo-hydrogen at C_7) and 5 (exo-hydrogen at C_6 and endo-hydrogen at C_7) was confirmed on

the basis of NMR spectra after conversion to 5-oxo bromo ether 6 and 7, [6] respectively, and from the consideration of the trans addition pathway for bromo ether formation. In the nomenclature developed by Baldwin,[5] the bromo ether formation giving 4 and 5 is an example of a 5-endo-trig ring closure, which is a rather unfavorable cyclization. The cyclization between C_6 and C_9-OH was confirmed after conversion of 4 and 5 to 6,9-epoxy diene 10[7] on tosylation with p-toluenesulfonyl chloride-pyridine followed by treatment with 1,5-diazabicyclo[5,4,0]undec-1-ene(DBU).

Oxidation of 5-hydroxy bromo ether 4 and 5 with collins' reagent[8] gave 5-oxo bromo ether 6 (84%) and 7 (81%)(observed Rf values on silica gel TLC plates with ethyl acetate-cyclohexane 4:5 as eluent, 0.52 for 6 and 0.63 for 7), respectively. Treatment of 5-oxo bromo ether 6 and 7 with excess DBU in tetrahydrofuran (30 mL/g of 6 and 7) at ambient temperature instantaneously afforded a single product, 5-oxo enol ether 8 (78% from 6 and 65% from 7, respectively). The structure of 8 was established on the basis of NMR,IR and Mass spectrum.[9] Methanolysis of 5-oxo enol ether 8 with sodium methoxide in anhydrous methanol at ambient temperature for one day gave the corresponding 5-oxo enol ether 9 in a quantitative yield.[10]

The 5-oxo enol ether 9 was hydrolyzed with aqueous sodium hydroxide in methanol. The mixture was acidified with hydrochloric acid and extracted with ethyl acetate to afford free carboxylic acid 2 (84%).[11]

6,7-Dehydro-5-oxo-prostaglandin I_1 2 is more stable than PGI_2, owing to the conjugation of enol ether linkage,but shows only weak activity in inhibition of rabbit platelet aggregation(0.01 as active as PGE_1),probably because of preferential s-trans conformation of α,β-unsaturated ketone group.

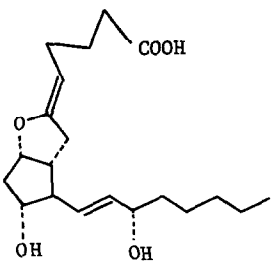
References and Notes

1) Synthesis of prostaglandins and their congeners. Part VII. for Part VI see K.Ohno and H.Nishiyama, Tetrahedron Letters , accepted for publication.

2) H.Nishiyama and K.Ohno, Chemistry Letters,661(1979). Part V.

3)a) K.C.Nicolaou, G.P.Gasic, W.E.Barnette, Angew.Chem.,Int.Ed.Engl.,17, 293(1978).

b) S.Moncada, R.J.Gryglewski, S.Bunting and J.R.Vane, Nature, 263, 663



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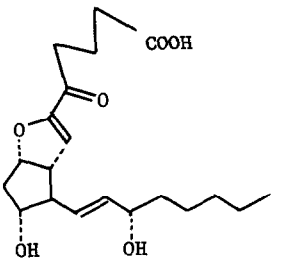

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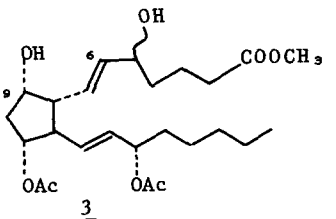

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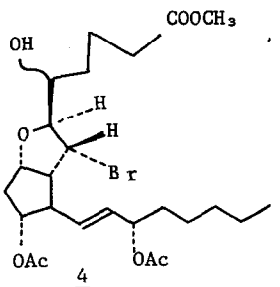

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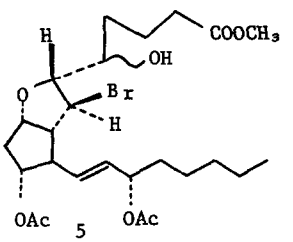

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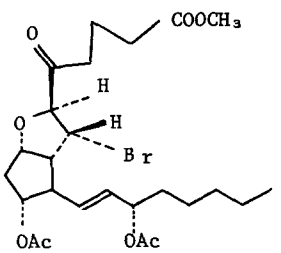

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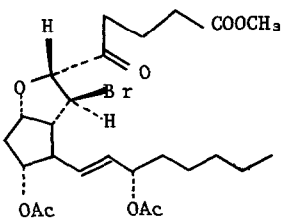

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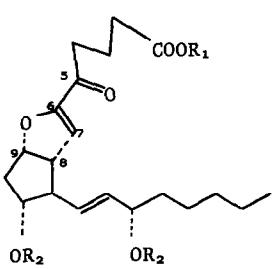


8 $R_1 = CH_3$, R_2 = Ac

9 $R_1 = CH_3$, R_2 = H

(1976).

c) R.J.Gryglewski, S.Bunting, S.Moncada, R.J.Flower and J.R.Vane, Prostaglandins, 12,685(1976).

d) R.J.Gryglewski, R.Korbut and A.Ocetkiewicz, Prostaglandins,15,637(1978).

e) S.Moncada, R.J.Gryglewski, S.Bunting and J.R.Vane, Prostaglandins,12, 715(1976).

f) B.J.R.Whittle, N.K.Boughton-Smith, S.Moncada and J.R.Vane, Prostaglandins, 15,955(1978).

4) 4: IR(ν cm^{-1})3600~3300,2920,2850,1735,1430,1240,1010,965,885, NMR($CDCl_3$, δ ppm)0.9(t,3H), 1.2~1.9(m,14H), 2.04(s,3H), 2.06(s,3H), 2.38(t,2H), 2.1~2.8(m,3H), 3.04(s,3H), 3.86(m,1H), 4.08(dd,1H), 4.35 (t,1H), 4.58(m,1H), 4.82(m,1H), 5.2(m,1H), 5.58(m,2H), MS(m/e)548,546. 5: IR(ν cm^{-1})3600~3300,2920,2850,1735,1430, NMR($CDCl_3$, δ ppm)0.9(t,3H), 1.2~1.9(m,14H), 2.04(s,3H), 2.06(s,3H), 2.38(t,2H),2.1~2.8(m,4H),3.64 (s,3H), 4.10(dt,1H), 4.60(m,1H), 4.92(m,1H), 5.17(m,1H), 5.53(m,2H), MS(m/e)548,546.

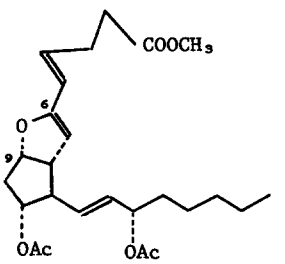
5) J.E.Baldwin, J.Chem.Soc.,Chem.Commun., 734(1976).

6) 6: NMR($CDCl_3$, δ ppm) 4.32(d,1H,$J_{H(C_7)-H(C_8)}$= 8.0 Hz,H(C_7)), 4.46(s,1H, H(C_6)), 7: NMR($CDCl_3$, δ ppm) 4.26(dd, 1H, $J_{H(C_7)-H(C_6)}$= 5.2 Hz, $J_{H(C_7)-H(C_8)}$= 3.0 Hz, H(C_7)), 4.56(d, 1H, $J_{H(C_6)-H(C_7)}$ = 5.2 Hz,H(C_6)).

7) The 6,9-epoxy diene 10 was proved to be identical with an authentic sample. see 1) Part VI.

8) J.C.Collins, W.W.Hess, F.J.Frank, Tetrahedron Letters, 3363(1968).

9) 8: TLC(silica gel, ethyl acetate-cyclohexane 4:5 as eluent)Rf= 0.57, IR(ν cm^{-1})1735,1690,1640,965, NMR($CDCl_3$, δ ppm)0.9(t,3H),1.2~1.7 (m,12H),2.0(m,1H),1.94(s,3H),2.04 (s,3H),2.36(t,2H),2.68(t,2H),3.30 (m,1H),3.64(s,3H),4.86(m,1H),5.14 (m,2H),5.5(m,2H),5.90(d,1H,J=3.0 Hz, H(C_7)). MS(m/e) 464(M^+).



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10) 9: TLC(silica gel, ethyl acetate as eluent)Rf = 0.42, IR(νcm^{-1}) 3600~3300, 1735,1690,1640, NMR($CDCl_3$, δ ppm) 5.96(d,1H, J= 3.0 Hz, H(C_7)), MS(m/e)380(M^+),362,349,280.

11) 2: TLC(silica gel, ethyl acetate- 2-propanol -water 91:8:1) Rf= 0.42, IR(ν cm^{-1})3600~2500, 1700,1690,1640, NMR($CDCl_3$, δ ppm) 5.90(d,1H, J= 3.0 Hz, H(C_7)).

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