Tetrahedron Letters No. 32, pp 3003 - 3004.

0040-4039/79/0801-3003$02.00/0

4,5,6,7-TETRADEHYDRO-PGI_1, A STABLE AND POTENT INHIBITOR OF BLOOD PLATELET AGGREGATION[1)]

Kiyotaka Ohno * and Hisao Nishiyama
Basic Research Laboratories, Toray Industries Inc.,
Tebiro, Kamakura 248, Japan

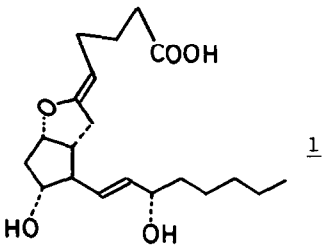
ABSTRACT The titled compound, which is a stable and potent analog of PGI_2, was synthesized from easily available enone 3 in two steps.

Since the discovery of prostacyclin (PGI_2, 1) by Vane and his associates[2)], increasing numbers of analogs have been reported[3)]. PGI_2 has potent biological activities including inhibition of blood platelet aggrgation[2)4)], de-aggregation of platelet thrombi[5)], vasodilation[2)] and inhibition of gastric acid secretion[6)], but is unstable even under the neutral condition because of the presence of enol ether linkage[7)]. To date several stable analogs of PGI_2 with similar activity have been reported in search of therapeutically useful biomimic of PGI_2. Among these are Δ^6-prostacyclin[8)], 6,9-thiaprostacyclin[9)], 6,9-methano-prostacyclin[10)], 6,9-azaprostacyclin[11)] and 6,9-pyridazaprostacyclin[12)]. We wish to report a stable analog of PGI_2, 4,5,6,7-tetradehydro-PGI_1 which is a potent inhibitor of blood platelet aggregation.

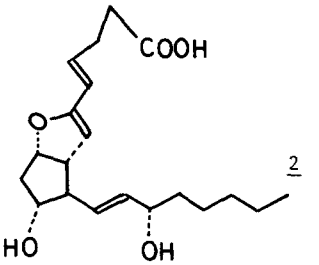
Easily available 4,5-didehydro-11(O),15(O)-diacetyl-6-oxo-$PGF_{1\alpha}$methyl ester 3 [1)] in dimethoxyethane was treated with anhydrous p-toluenesulfonic acid at ambient temperature for 10 minutes to afford 4,5,6,7-tetradehydro-11(O),15(O)-diacetyl-PGI_1 methyl ester 4 (88%). The structure of diene 4 was established on the basis of IR (ν cm^{-1}, 1740, 1680, 1600), NMR (δ ppm, $CDCl_3$, 0.9(m,3H), 1.2~1.8(m,10H), 1.97(s,3H), 2.05(s, 3H), 2.3~2.7(m,5H), 3.14 (m,1H), 3.68(s,3H),4.8~5.3(m,4H), 5.50(m,2H), 5.59(s,3H)) and mass spectrum (m/e, 448(M^+), 388(M^+-60), 328(M^+-120)). Methanolysis of diene 4 with sodium methoxide in anhydrous methanol at ambient temperature for one day gave the corresponding diene 5 (68.8%) after purification by silica gel column chromatography (ethyl acetate:water:triethyl amine = 97:2:1 as eluent) [13)].

Diene 4 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 (86.5%)[14)].

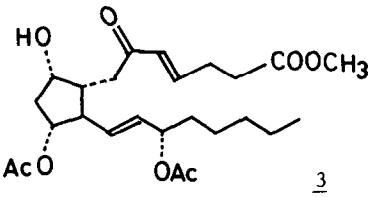
4,5,6,7-Tetradehydro-PGI_1 2 is more stable than PGI_2, owing to the conjugation of enol ether linkage, and showed nearly the same potency as PGE_1 in the inhibition of rabbit platelet aggregation induced by arachidonic acid[15)].



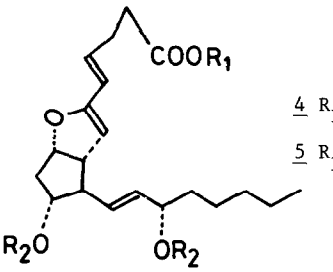
1



2



3



4 R_1= CH_3, R_2= Ac

5 R_1= CH_3, R_2= H

REFERENCES AND NOTES

1) Synthesis of prostaglandins and their congeners. Part VI. for Part V see Hisao Nishiyama and Kiyotaka Ohno, Chemistry Letters , in press.

2) S.Moncada, R.J.Gryglewski,S.Bunting and J.R.Vane, Nature, 263,663(1976).

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

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

5) a) R.J.Gryglewski, R.Korbut and A.Ocetkiewicz, Prostaglandins,15,637(1978).
b) S.Moncada, R.J.Gryglewski, S.Bunting and J.R.Vane, Prostaglandins,12,715(1976).

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

7) M.J.Cho and M.A.Allen, Prostaglandins,15,943(1978).

8) K.Shimoji, Y.Konishi, Y.Arai, M.Hayashi, and H.Yamamoto,J.Am.Chem.Soc.,100,2547(1978).

9) a) K.C.Nicolaou, M.E.Barnette, G.P.Gasic, and R.L.Magolda,J.Am.Chem.Soc.,99,7736(1977).
b) M.Shibasaki and S.Ikegami, Tetrahedron Letters, 559(1978).

10) a) K.Kojima and K.Sakai, Tetrahedron Letters, 3743(1978). b) M.Shibasaki, J.Ueda, and S.Ikegami, Tetrahedron Letters,433(1979). c) K.C.Nicolaou, W.J.Sipio, R.L.Magolda, S.Seitz and W.E.Barnette, J.C.S.Chem.Comm.,1067(1978).

11) G.L.Bundy, and J.M.Baldwin, Tetrahedron Letters.,1371(1978).

12) K.C.Nicolaou, W.E.Barnette, R.L.Magolda, J.Am.Chem.Soc.,101,766(1979).

13) 5 : m.p. 58~60°C, IR(ν cm^{-1}) 3600 3100,2920,2850,1740,1665,1603,1435,1360,1240,1010,960, 910, ^{1}H-NMR($CDCl_3$,δ ppm) 0.90(t,3H),1.2~1.6(m,10H),2.2~2.6(m,8H),3.65(s,3H),3.75(m,1H), 4.00(m,1H),4.87(d,1H),4.89(m,1H),5.50(m,2H),5.91(s,2H), MS(m/e) 364(M^+),305,263.

14) 2 : IR(ν cm^{-1}) 3600~2500,2920,2850,1700,960,^{1}H-NMR($CDCl_3$,δ ppm) 0.9(t,3H), 1.2~1.6(m,10H), 2.2~2.6(m,6H),3.75(m,1H),3.90(m,1H),4.85(d,1H),4.86(m,1H),5.2(b,3H),5.50(m,2H),5.90(s,2H).

15) Tests on platelet aggregation were carried out by Mr.S.Nishio in our laboratories.

(Received in Japan 28 April 1979)