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SYNTHETIC ENTRY INTO A NEW TYPE OF PROSTAGLANDIN: 6(9α),6(11α)-DIOXIDO-15S-HYDROXYPROST-13E-ENOIC ACID METHYL ESTER

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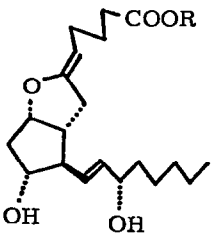
The successive discovery of thromboxane A_2[1] and prostacyclin (PGI_2) (1g)[2], both of which play important roles in blood clotting[3], suggests, at a standpoint of prostaglandin biosynthesis, an existence of other compounds related to them. In connection with Pace-Asciak's work[4] in discovering one of prostacyclin isomer (2), whose structure has very recently been claimed as 3a by Sih and Huang[5,6], we have undertaken to examine the chemical reactivity of prostacyclin methyl ester (1b) under anhydrous acidic condition[7]. In this communication, we describe a first synthesis of 6(9α),6(11α)-dioxido-15S-hydroxyprost-13E-enoic acid methyl ester (4b).

Prostacyclin methyl ester (1b) synthesized according to the reported procedure[8] was treated with a catalytic amount of anhydrous p-toluenesulfonic acid[9] in dry benzene (0.5 hr, room temperature, under argon). After quenching by the addition of a saturated sodium bicarbonate solution, the mixture was worked up in the usual manner, followed by purification by column chromatography over Florisil using solvents containing triethylamine (0.1% sufficient). A nearly colorless oil, which we identified as 4b, was obtained in 50-60% yield with a small amount of 6-oxo-$PGF_{1\alpha}$ methyl ester (6b)[10].

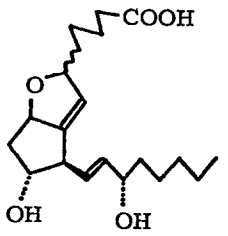
The structure 4b was determined on the following bases: TLC (silica gel, methylene chloride-methanol (95:5)), Rf 0.17 for 1b, 0.32 for 4b; ^{1}H-NMR ($CDCl_3$, δ)[11], 5.40 (m, 2H, -CH=CH-), 4.77 (m, 1H, Hc), 4.32 (m, 1H, Hb), 4.00 (m, 1H, Ha); IR (ν, film), 3460 cm-1 (OH, a medium absorption corresponding to 1 OH), no vinylic ether absorption; Mass (m/e), 366 [M^+], 348 [M^+-H_2O]. In order to confirm the structure 4b, the dioxido compound (4b) was oxidized with manganese dioxide in anhydrous methylene chloride to the enone (5)[12]; TLC (silica gel, methylene chloride-methanol (95:5)), Rf 0.52; ^{1}H-NMR ($CDCl_3$, δ), double doublets of doublet centered at 6.54 and 6.16 (olefinic AB protons of ABX pattern, J_{AB}=16.1 Hz, J_{BX}= 5.6 Hz, J_{AX} = 1.3 Hz, 2H, He and Hd), 4.76 (m, 1H, Hc), 4.43 (m, 1H, Hb); Mass (m/e), 364 [M^+].

Independent evidence for the structure 4b was also obtained by the extremely facile and clean hydrolysis of 4b under aqueous acidic conditions to a more polar substance of Rf 0.11 (methylene chloride-methanol (9:1)), which was characterized as 6-oxo-$PGF_{1\alpha}$ methyl ester (6b) by the spectral and TLC comparisons with the authentic material[13].

In this reaction, it is expected that the oxonium ion (7) is incipiently formed by protonation to the vinylic



1a : R = H
1b : R = CH_3



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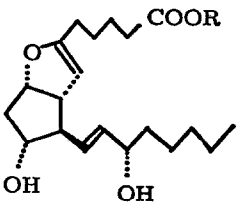
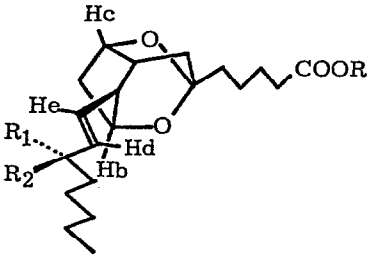
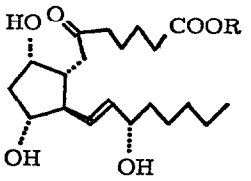


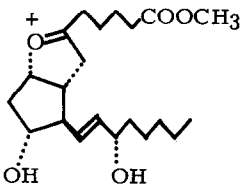
3a : R = H
3b : R = CH_3



4a : R = H, R_1 = OH, R_2 = H
4b : R = CH_3, R_1 = OH, R_2 = Ha
5 : R = CH_3, R_1 - R_2 = O



6a : R = H
6b : R = CH_3



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ether group. Considering the structural relationship in 1b[14], the contribution of the neighboring group participation by 11α-hydroxy group would be predictable. However, isolation of the tricyclic ketal isomer (4b) in significant yield must be a rather surprising result.

The isolation of 4b[15] converted from 1b under anhydrous condition is particularly instructive in considering the further transformation of 1a or the presence of the isomers in biological system[16]. At present, it should be emphasized that there are two relatively unstable substances (1b and 4b) which are rapidly hydrolyzed to 6-oxo-PGF1α methyl ester (6b) under aqueous acidic condition and these results suggest that the ketal isomer (4a) may be obtainable from biological reactions.

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References and Notes

† Visiting scientist from Kotobuki Pharmaceutical Company, Sakaki-machi, Nagano, 1978.

†† Visiting scientist from the Faculty of Pharmaceutical Sciences, Teikyo University, 1977-1978.

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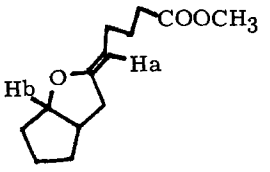
6. After completion of our study, the authors knew the report (Ref. 5) concerning reconsideration of the structure 2. We also have had doubt to the structure 2, especially in its pmr assignment, its highly strained structure, and its biosynthetic pathway, and presumed the structure 3a instead of 2 from the results of the isomerization study of the model system (Ref. 7).

7. In model studies, the transformation of 8 to 9 is successful. Although 8 is less stable than 1b, 9 is found to be a fairly stable substance.



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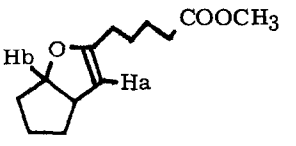

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Spectral data of 8 and 9 are as follows: 8: IR (ν, film); 1690 cm-1 (enol ether), ^{1}H-NMR ($CDCl_3$, τ); 4.02 (triplet, J = 7 Hz, Ha), 4.74 (multiplet, Hb), Mass (m/e); 224 [M^+]. 9: IR (ν, film); 1670 cm-1 (enol ether), ^{1}H-NMR ($CDCl_3$, τ); 4.36 and 4.80 (multiplet, Ha or Hb), Mass (m/e); 224 [M^+].

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d, N. Whittaker, ibid., 2805 (1977); e, K. C. Nicolaou, W. E. Barnette, G. P. Gasic, R. L. Magolda, and W. J. Sipio, Chem. Comm., 630 (1977).

9. Azeotroped 3 times by rotary evaporation of dry toluene before using.

10. The formation of 6b is considered to be due to the presence of a trace amount of water in the reaction mixture. The dimeric form of 1b for the product could be excluded by field desorption mass spectroscopy.

11. The assignments were done by means of decoupling techniques.

12. 5 can be purified by column chromatography over Florisil using solvents containing triethylamine (0.1% sufficient).

13. Prepared by the acid-catalyzed hydrolysis of 1b.

14. For the steric relationship of prostacyclin, see J. Fried and J. Barton, Proc. Natl. Acad. Sci. USA, 74, 2199 (1977) and I. Tömösközi, G. Galambos, G. Kovács, and L. Radics, Tetrahedron Letters, 581 (1978).

15. Preliminary biological examination showed that 4b did not inhibit human platelet aggregation. The study of other biological activities are now in progress.

16. As is shown in the following scheme, the formation of new compounds from 4b could be possible.