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THE SYNTHESIS OF NITROGEN-CONTAINING PROSTACYCLIN ANALOGS

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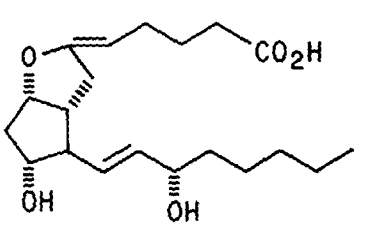
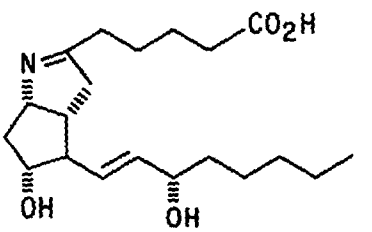
Prostacyclin[1,2] (formerly called PGX, now PGI_2) constitutes the most recently discovered addition to the family of biologically potent, unstable metabolites of arachidonic acid formed via the endoperoxide PGH_2. The predominant metabolite of PGH_2 in blood vessel walls, prostacyclin is more potent than PGE_1 or PGD_2 as an inhibitor of platelet aggregation. However, biological evaluation of compounds like the endoperoxides or prostacyclin is complicated by the relative instability of these substances in aqueous solution. In the case of PGH_2, this problem has been partially circumvented by the use of chemically more stable analogs such as cyclic ethers[3], azo analogs[4] and disulfides[5], which exhibit biological effects similar in many respects to PGH_2 itself, but which cannot be converted enzymatically into the usual array of PGH_2 metabolites. Likewise, we felt that studies currently underway to elucidate the physiological role of prostacyclin and its relationship to other arachidonic acid metabolites would be aided by the availability of prostacyclin analogs which closely resembled PGI_2 in shape, polarity and, hopefully, biological profile, but which possessed greater chemical and metabolic stability.[14]

In this report, we describe the synthesis of 9-deoxy-9α,6-nitrilo-$PGF_1\alpha$ 1 and the corresponding cyclic amines in which the oxygen atom of prostacyclin has been replaced by nitrogen.



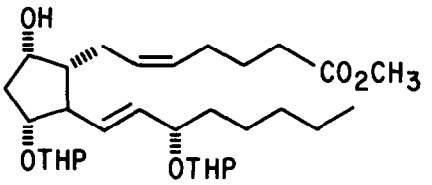
PGI_2



1

Nitrilo analog 1 should be similar in polarity to PGI_2, and its sp_2 hybridization at C-6 should allow it to adopt similar conformations as well.

As outlined in Figure I, $PGF_2\alpha$ methyl ester, 11,15-bis(tetrahydropyranyl ether) 2 was first converted to the 9β-epimer 4 with triphenylphosphine, benzoic acid and diethyl azodicarboxylate in tetrahydrofuran[6,7], followed by treatment of the resulting 9β-benzoate[8] 3 with methanolic sodium methoxide. The overall yield of this two-step inversion sequence was 70%. Olefins resulting from elimination at C-9 invariably accompanied the desired product to the extent of 10-20%. This by-product could be minimized by adding the diethyl azodicarboxylate as rapidly as



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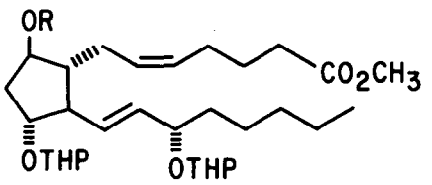
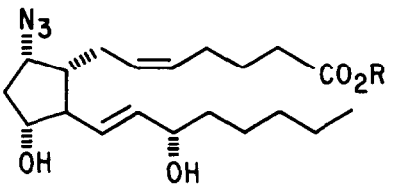
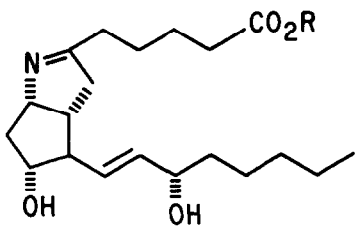


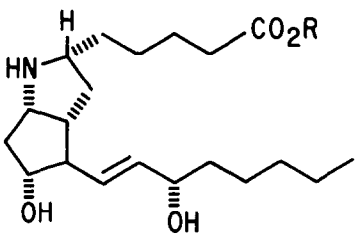
3, R = COϕ
4, R = H
5, R = Ts



6, R = CH_3
7, R = H



8, R = CH_3 (mp 52-54°)
1, R = H
9, R = H, HCl salt (mp 72-76°)



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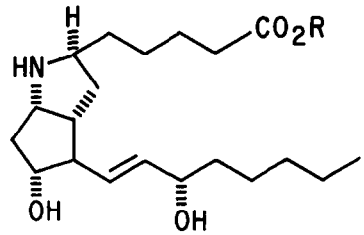


10, R = CH_3 (mp 114-115°)
11, R = H (mp 186-188°)

12, R = CH_3 (mp 116-117°)
13, R = H (mp 186-189°)

FIGURE I

physically possible to a cooled, stirred solution of the other reactants. Tosylation of the 9β-hydroxyl (toluenesulfonyl chloride, pyridine, 18 hr, 25°) and tetrahydropyranyl ether hydrolysis (acetic acid, water, tetrahydrofuran, 40°, 3 hr) afforded the C-9 monotosylate of $PGF_2\beta$ in 60% yield. Displacement of the 9β-tosylate with sodium azide in hexamethylphosphoramide (40°, 2 hr) yielded 9α-azide 6[8] (essentially quantitative), which upon heating at 70-80°C for 16 hr, either neat or in ethyl acetate, dimethylformamide or dimethoxyethane solution gave crystalline cyclic imine 8 (80% yield over two steps).[9]

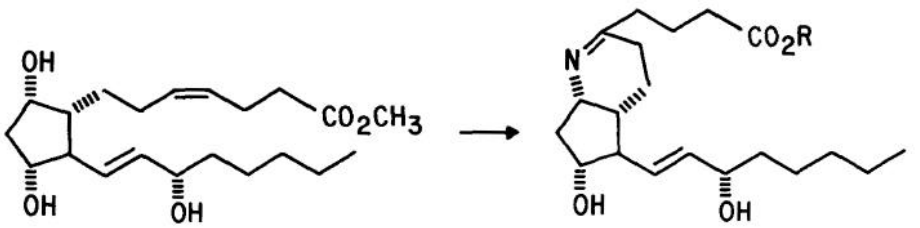
This cycloaddition reaction also proceeded at room temperature or below, but so slowly (~ 5% in 3 days at 25°) that it was not preparatively useful. Even at the higher temperature, the cycloaddition/N_2 elimination was very clean. No product other than imine 8 was evident on thin layer chromatographic examination of the crude reaction mixture.

The corresponding acid 1 could be obtained either by hydrolysis of ester 8 (followed by XAD-2 resin purification of water-soluble 1), or preferably by hydrolysis of azide ester 6. The acid 7, easily purified and not water soluble, was then subjected to thermal cyclization, yielding imine acid 1 - an amorphous, water-soluble semi-solid, zwitterionic to the extent of about 30%. The 1640 cm^{-1} infrared band observed in acid 1 and ester 8 is typical of 2-alkyl-1-pyrrolines.[10] The slightly hygroscopic hydrochloride salt 9 formed readily, and in fact both imines 8 and 1 were stable in 1M hydrochloric acid for 3 hr at 25°. (After 24 hr, about 15% decomposition to less polar products.)

Mild acylation of nitrilo ester 8 (acetic anhydride, pyridine, 25°, 18 hr), followed by acid hydrolysis (0.05M HCl, 4:1 THF/H_2O, 1 hr, 25°) afforded 9α-acetamido-11α,15S-diacetoxy-6-oxo-prost-13Z-enoic acid (mp 107.8-108.5°, M^+ obs. 509.2982; theor. for $C_{27}H_{43}NO_8$ 509.2988) in excellent yield.

Reduction of imine ester 8 yielded amino esters 10 and 12, which could be purified chromatographically (silica gel; 85 chloroform, 15 methanol, 2 triethylamine; 10 r_f 0.40; 12 r_f 0.34). Each isomer was then hydrolyzed to the corresponding crystalline amino acid (11 and 13 respectively, both completely zwitterionic) and the latter were purified on an XAD-2 resin column (elution with water to remove salts, then methanol to elute the amino acid). The stereochemical assignments at C-6 in amines 10 and 12 were made by comparison of their ^{13}C nmr spectra with those of the two isomers of 5,6-dihydro-PGI_2 (PGI_1), which in turn have been identified unequivocally by chemical means.[11] In both the oxygen and nitrogen cases, the C-6 and C-9 signals of the more polar (6S) isomer are shifted upfield relative to the less polar (6R) isomer.

Using a reaction sequence similar to that described above for the synthesis of cyclic imine 1, cis-Δ^4-$PGF_1\alpha$ methyl ester 14[12] could be converted in six steps[8] to the 9α,5-nitrilo analogs 15 and 16. In this case, the C-11 and C-15 hydroxyls were protected as t-butyldimethylsilyl ethers[13] (5% excess of reagents, 2 hr, 0°, 71% yield) instead of tetrahydropyranyl ethers. Cyclization of the 9α-azide corresponding to 14 proceeded much more slowly (80°, 44 hr) and in lower yield (44%) here than with the five-membered ring isomer. The C=N absorption at 1660 cm^{-1} in the infrared spectrum of 15 is consistent with the six membered ring imine structure.[10]



14

15, R = CH_3
16, R = H

Nitrilo analogs 1 and 9 are essentially equivalent to prostacyclin in their ability to inhibit PGH_2-induced or ADP-induced platelet aggregation in human platelet-rich plasma.[15]

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