is $\sigma_{\parallel} \sim 3.3\ (\Omega\ cm)^{-1}$, only ~5-fold less than that of the $y = 0.35$ material. Near and below room temperature the conductivity is activated, also with an activation energy extrapolated to 0 K of $\Delta(0) \sim 50$ meV. Moreover, the qualitative shapes of the plots of $\sigma(T)$ are in fact quite similar for both compositions. As the temperature is increased above ambient, $\sigma_{\parallel}(T)$ for $Ni(OMTBP)(I_3)_{0.97}$ also shows a broad conductivity maximum, but with $T_m \sim 340$ K, roughly 40–60 K greater than T_m for the $y = 0.35$ phase. Again, for different $y = 0.97$ preparations, T_m will vary and $\sigma_{\parallel}^m$ is inversely related to T_m.[21]

Both the room temperature value of $\sigma_{\parallel}$ and the shape of the $\sigma_{\parallel}(T)$ vs. T curve for $Ni(Pc)(I_3)_{0.33}$ differ sharply[10] from the results for $Ni(OMTBP)(I_3)_{0.35}$. This shows that apparently modest chemical variations in the macrocycle structure can substantially alter the physical characteristics of a partially oxidized ML system. In contrast, the differing degrees of oxidation for the two materials based on Ni(OMTBP) apparently lead rather to a quantitative difference in the response of $\sigma_{\parallel}$ vs. T. However, the change in properties with increased oxidation must reflect any structural alteration as well as the electronic difference. A fuller understanding of the dependence of conductivity on the degree of oxidation must thus await further studies and the complete crystal structure determinations.

Acknowledgments. We thank Professor J. A. Ibers and Dr. R. P. Scaringe for crystallographic data regarding the $Ni(Pc)(I)_x$ and $Ni(OMTBP)(I)_x$, Mr. C. J. Schramm for assistance in material preparation and many helpful discussions, and Professor T. J. Marks for discussion of the Raman spectra. This work has been supported by the Materials Research Center of Northwestern University (NSF-GH-33575).

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(21) We report the high-temperature behavior ($T \leq 370$ K) of the $y = 0.97$ composition with some caution, as the conductivity curve is not wholly reproduced upon cycling, suggesting the possibility of some crystal degradation and/or chemical reaction with the contacts. Observations of I_2 loss indicate that these crystals are stable up to 380 K and possibly for 390 K, at least for ~0.5 h; I_2 is lost at 400 K, yielding crystals whose appearance is is that of the $y = 0.35$ material.

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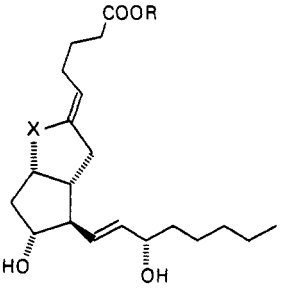
6,9-Thiaprostacyclin. A Stable and Biologically Potent Analogue of Prostacyclin (PGI_2)

Sir:

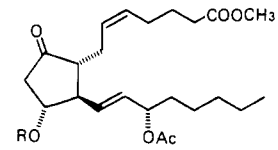
The discovery of prostacyclin (PGI_2, **1**)[1] late in 1976 has not only revolutionized current concepts in cardiovascular research[2] but has also thrust this molecule into the forefront of biological and chemical research.[3] Although several syntheses[4-6] have made it readily available, its unstable nature encumbers biological studies and makes it a doubtful pharmacological agent. In light of its biological importance, the synthesis of stable physiological mimics deserves a high priority. Even though some analogues of this molecule have been reported,[7] prostacyclin is at least two hundred times more potent than the most active of these substances.[8,9] In this communication we report the synthesis and preliminary biological properties of a potent and relatively stable analogue of prostacyclin (PGI_2), namely 6,9-thiaprostacyclin (**2**).



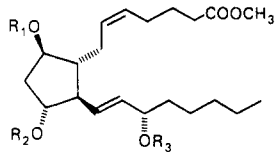
1, X = O, R = H
2, X = S, R = H
3, X = S, R = CH_3 or C_2H_5

The methyl ester of 15-acetoxy PGE_2 (**4**)[10] was converted to its tetrahydropyranyl ether (**5**)[11] with dihydropyran (1.5 equiv) under acid (*p*-toluenesulfonic acid) catalysis in methylene chloride at 25 °C (100% yield) and reduced with excess zinc borohydride (DME, 25 °C, 15 h) to afford the 9β-$PGF_{2\alpha}$ derivative **6**, as the major product together with the 9α isomer (9β:9α ratio, 55:45) in 95% total yield. Chromatographic purification of **6** (silica; ether; 9β, R_f 0.47; 9α, R_f 0.59) followed by treatment with methanesulfonyl chloride (1.2 equiv) in methylene chloride at −20 °C in the presence of triethylamine led to the mesylate **7** (100%). When **7** was exposed to excess potassium thioacetate in dimethyl sulfoxide at 45 °C for 24 h the thioacetate **8** was formed in 90% yield. Removal of the tetrahydropyran protecting group with acetic acid–tetrahydrofuran–water (3:2:2) at 45 °C (20 h) resulted in the formation of diacetate **9** (98% yield), which, in turn, yielded 9-thio $PGF_{2\alpha}$ methyl ester (**10**) upon treatment with anhydrous potassium carbonate (4 equiv) in absolute methanol at 25 °C (yield, 83%).

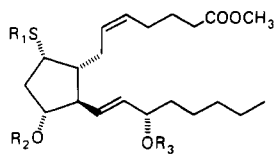
A second route to 9-thio $PGF_{2\alpha}$ methyl ester (**10**), the first key intermediate for the synthesis of 6,9-thiaprostacyclin (**2**), was developed starting with the readily available 11,15-bis(tetrahydropyranyl) ether $PGF_{2\alpha}$ methyl ester (**11**).[12] This



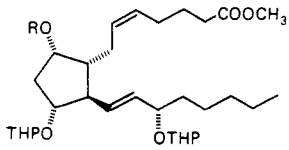
4, R = H
5, R = THP



6, R_1 = H, R_2 = THP, R_3 = Ac
7, R_1 = SO_2CH_3, R_2 = THP, R_3 = Ac
13, R_1 = H, R_2 = R_3 = THP
14, R_1 = SO_2CH_3, R_2 = R_3 = THP



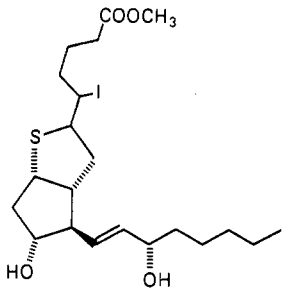
8, R_1 = R_3 = Ac, R_2 = THP
9, R_1 = R_3 = Ac, R_2 = H
10, R_1 = R_2 = R_3 = H
15, R_1 = Ac, R_2 = R_3 = THP
16, R_1 = Ac, R_2 = R_3 = H



11, R = H
12, R = $SO_2C_6H_5$ or SO_2CH_3

material was transformed to its 9 epimer (**13**) via its tosylate (**12**, R = $SO_2C_6H_5$) or preferably its mesylate (**12**, R = SO_2CH_3) using a previously reported procedure[13] by displacement with potassium superoxide, and subsequently mesylated quantitatively (methanesulfonyl choloride, triethylamine, methylene chloride, −20 °C) to afford **14**. Excess potassium thioacetate in dimethyl sulfoxide at 45 °C converted the mesylate **14** to the thioacetate **15** in 91% yield. On exposure to acetic acid–tetrahydrofuran–water (3:2:2) at 45 °C for 20 h, **15** suffered the loss of its tetrahydropyran protecting groups leading to **16** (yield, 89%). This thioacetate was then converted to 9-thio $PGF_{2\alpha}$ methyl ester (**10**, 80% yield) with anhydrous potassium carbonate (2 equiv) in absolute methanol (25 °C, 20 h).

Addition of iodine (1.1 equiv) to a methylene chloride solution of the now readily available 9-thio $PGF_{2\alpha}$ methyl ester (**10**)[14] in the presence of potassium carbonate (2 equiv) at −40 to 0 °C led to the iodide **17**[15] as the major product (55%),



17

presumably via the intermediate sulfenyl iodide undergoing a facile intramolecular addition to the 5,6 double bond. The iodo thiaether **17** on exposure to excess 1,5-diazabicyclo[5.4.0]undec-5-ene in benzene at 80 °C (1 h) was transformed cleanly and in essentially quantitative yield to 6,9-thiaprostacyclin methyl ester (**3**, R = CH_3).[15,16] The same transformation could be carried out, although less cleanly, employing excess sodium methoxide in absolute methanol or sodium ethoxide in ethanol (leading to **3**, R = CH_2CH_3). Hydrolysis of the esters **3** in 90% ethanol containing sodium ethoxide (5 equiv) afforded quantitatively stable solutions of 6,9-thiaprostacyclin (**2**) as its sodium salt ready for bioassays. Both the acid **2** and methyl ester **3** could be isolated from pH 4 buffers by extraction with ether. They showed increased stability compared with prostacyclin (**1**) in neutral solutions or neat and could be chromatographed[17] on silica gel without appreciable decomposition.

The *Z* geometry of the enol ether double bond in **3** and **2** was based on mechanistic considerations for the formation and dehydroiodonation of intermediate **17** and was supported by the biological properties of **2** and comparisons of their ^1H NMR spectra with those of **1** and its methyl ester.

6,9-Thiaprostacyclin (**2**) has very interesting and divergent biological properties. It shows, for example, comparable potency to natural prostacyclin (**1**) in inhibiting platelet aggregation,[18] thus being the most active of the prostacyclin mimics. However, 6,9-thiaprostacyclin inhibitory activity does not diminish when kept in neutral saline solution for several hours while the activity of PGI_2 is virtually abolished. In contrast to the vasodilatory effects of prostacyclin, the thia analogue is a potent vasoconstrictor of isolated cat coronary artery.[19,20] In this regard, it mimics the endoperoxides (PGG_2 and PGH_2) and thromboxane A_2. Its higher stability and unique combination of biological properties make this molecule a powerful tool in biological studies.[21,22]

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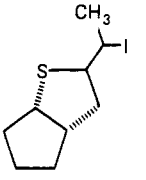
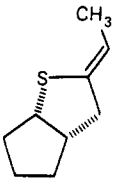


i



ii

(16) The ^1H NMR spectrum at 220 MHz in $CDCl_3$ showed the expected signals for the olefinic protons (τ 4.50 (m)) and the thioenol ether proton (4.72 (m)). The mass spectrum had a molecular ion peak at *m/e* 382.
(17) R_f values (silica gel, 5% methanol in ether): **17**, 0.51; **3**, 0.50; **2**, 0.16.

(18) Tests of platelet aggregation were carried out in collaboration with Professors J. B. Smith and M. J. Silver of the Cardeza Foundation, Thomas Jefferson University, Philadelphia, Pa. 19107.
(19) The effect of 6,9-thiaprostacyclin on isolated cat coronary artery was determined in collaboration with Mr. Martin Ogletree and Professor A. M. Lefer, Department of Physiology, Thomas Jefferson Medical College, Philadelphia, Pa. 19107.
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(21) Details on the biological properties of 6,9-thiaprostacyclin will be reported elsewhere.
(22) This research was supported by the University of Pennsylvania, Merck Sharp and Dohme, U.S.A., and Ono Pharmaceutical Co., Japan.

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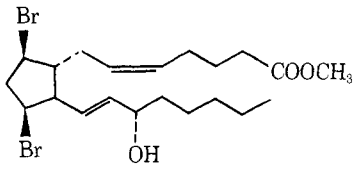
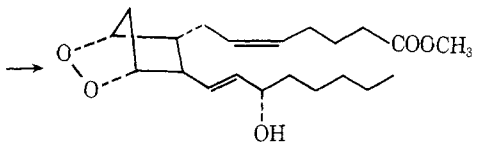
Synthesis of Prostaglandin H_2 Methyl Ester

Sir:

The prostaglandin (PG) endoperoxides, PGG_2 (**1**) and PGH_2 (**2**), are key intermediates in the bioconversion of arachidonic acid into a variety of physiologically active substances, including the prostaglandins,[1] thromboxane A_2,[2] 12-hydroxy-*cis*-5,*trans*-8,*trans*-10-heptadecatrienoic acid (HHT),[3] and prostacyclin (PGI_2).[4,5] Endoperoxides **1** and **2** were first isolated from biosynthetic preparations in 1973 and were characterized by chemical conversion into known, stable molecules.[6] More recently, the biosynthetic procedure has been modified and simplified to allow preparation of PGH_2 and PGH_1 on a multimilligram scale.[7] At the same time, several groups have reported preliminary results that clearly are aimed at providing a chemical synthesis of the endoperoxides.[8,9] In this report we outline the preparation of various 9,11-dihaloprostaglandins and describe the conversion of one of these, 9β,11β-dibromo-9,11-dideoxy-$PGF_{2\alpha}$ methyl ester (**3**), into prostaglandin H_2 methyl ester (**4**).



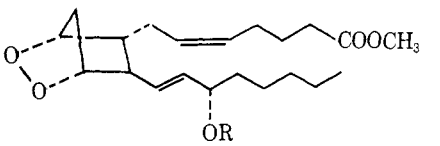
3



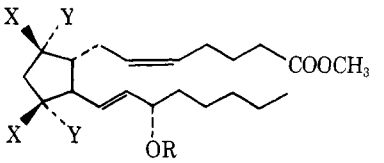
4

The following sequence of reactions was used to convert $PGF_{2\alpha}$ methyl ester (**5**), into the 9,11-ditosylate (**6**), the desired substrate for the preparation of 9,11-dibromoprostaglandins. Reaction of **5** and *n*-butylboronic acid (refluxing benzene, 2.5 h, azeotropic removal of water) gave the cyclic 9,11-*n*-butylboronic ester.[10] The 15-OH of this ester was derivatized with *tert*-butyldimethylsilyl chloride and imidazole (dimethylformamide, 40 °C, 20 h)[11] followed by removal of the cyclic 9,11-*n*-butylboronate with 30% aqueous hydrogen peroxide (acetone, 25 °C, 5 h) to give $PGF_{2\alpha}$ 15-*tert*-butyldimethylsilyl ether methyl ester (**7**). The ditosylate (**8**) of **7** was prepared by reaction of **7** with *p*-toluenesulfonyl chloride in pyridine and, following chromatography on silica gel, was hydrolyzed with 3:1:1 acetic acid–water–tetrahydrofuran to give **6.**

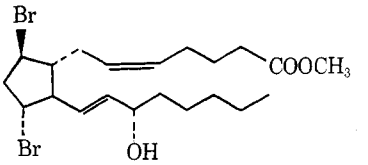
Reaction of **6** with lithium bromide (DMF, 65 °C, 1 h under N_2) followed by high pressure liquid chromatography on silica gel (15% acetone–hexane) gave, in increasing order of polarity



1, R = OH
2, R = H



5, X = R = H; Y = OH
6, X = R = H; Y = OTos
7, X = H; Y = OH; R = $OSi(CH_3)_2C(CH_3)_3$
8, X = H; Y = OTos; R = $OSi(CH_3)_2C(CH_3)_3$
10, X = R = H; Y = Br
11, X = Cl; Y = R = H
12, X = OTos; Y = R = H
13, X = R = H; Y = Cl



9

(silica gel TLC, 20% acetone in hexane), the following compounds as viscous oils. 9β,11α-Dibromo-9,11-dideoxy-$PGF_{1\alpha}$ methyl ester (**9**, 29% yield): R_f 0.33; mass spectrum (trimethylsilyl derivative), 564.1250, calcd for $C_{24}H_{42}{}^{79}Br_2O_3Si$ 564.1271, other ions at 549, 533, 521, 493, 485, 413, and 333 mass units. Anal. Calcd for $C_{21}H_{34}Br_2O_3$: Br, 32.33. Found: Br, 31.52. 9α,11α-Dibromo-9,11-dideoxy-$PGF_{2\alpha}$ methyl ester (**10**, 7.5%): R_f 0.27; mass spectrum (TMS derivative) 564.1272, remainder of spectrum nearly identical with that of **9.** Anal. Found: Br, 31.40. The desired **3**[12] (10%): R_f 0.25; mass spectrum (TMS derivative) 564.1261. Anal. Found: Br, 30.62. The order of appearance of these three products during the reaction, as detected by TLC, was **3** followed by **9** and then by **10.** One may reasonably expect formation of the 9β,11β isomer (**3**) to be kinetically most favored in this reaction, while the 9α,11α isomer will be least favored. Thermodynamically, the 9β,11α isomer (**9**), in which all substituents on the cyclopentane ring are trans, must be favored. These considerations lead to the tentative assignments of configuration given to the reaction products. These assignments were confirmed by comparison of the nuclear magnetic resonance (NMR) spectra of the dibromides with those of the dichlorides described below.

Reaction of 9α,11α-ditosylate **6** with lithium chloride (DMF, 65 °C, 2.5 h) gave a single dichloride (58% yield) that must be the 9β,11β-dichloro isomer **11**:[12] R_f 0.34 (20% acetone in hexane); mass spectrum (TMS derivative) 476.2279, calcd for $C_{24}H_{42}{}^{35}Cl_2O_3$ 476.2280. Anal. Calcd. for $C_{21}H_{34}Cl_2O_3$: C, 62.21; H, 8.45; Cl, 17.49. Found: C, 62.27; H, 8.91; Cl, 17.32. Likewise, reaction of lithium chloride with 11-epi-$PGF_{2\beta}$ methyl ester, 9,11-ditosylate (**12,** prepared from 11-epi-$PGF_{2\beta}$ methyl ester, by the same sequence of reactions used to prepare **6** from **5**) gave a single, isomeric dichloride (65% yield) that must be the 9α,11α-dichloro isomer **13**:[12] R_f 0.29 (20% acetone in hexane); mass spectrum (TMS derivative) 476.2279. Anal. Found: C, 62.72; H, 8.48; Cl, 17.91.

The NMR spectrum ($CDCl_3$) of 9β,11β-dibromo-9,11-dideoxy-15-keto-$PGF_{2\alpha}$ methyl ester (**14**,[12] obtained by Jones oxidation of **3** at −30 °C) (δ 6.81 (d of d, 1 H, J_{14} = 16 Hz, J_{12} = 8 Hz, $HC_{13}<$), 6.02 (d, 1 H, J_{13} = 16 Hz, $HC_{14}<$), 5.45 (m,