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Communications to the Editor

A New Stable Prostacyclin Mimic, 7-Oxoprostaglandin I_2

Sir:

Since the discovery of endogenous prostanoid PGI_2 (11) with highly potent antiaggregatory and vasodilating properties,[1] a great deal of synthetic effort has been devoted to the preparation of structurally modified analogues with increased stability against hydrolysis and metabolism.

Rapid disappearance of PGI_2 from the body is explained by a presumably nonenzymatic hydrolysis of the enol ether unit to produce 6-keto-$PGF_{1\alpha}$ and/or by enzymatic metabolism common to all the prostanoids involving steps such as oxidations at the 15-OH group and the β and ω positions of the chain and reduction of the 13,14 double bond. During the past decade with the investigation of many thousands of prostaglandin analogues, a certain "know-how" has been developed for the prevention or at least slowing down the enzymatic metabolism by structural modifications, e.g., $PGE_2 \rightarrow$ 15-Me-PGE_2, etc.

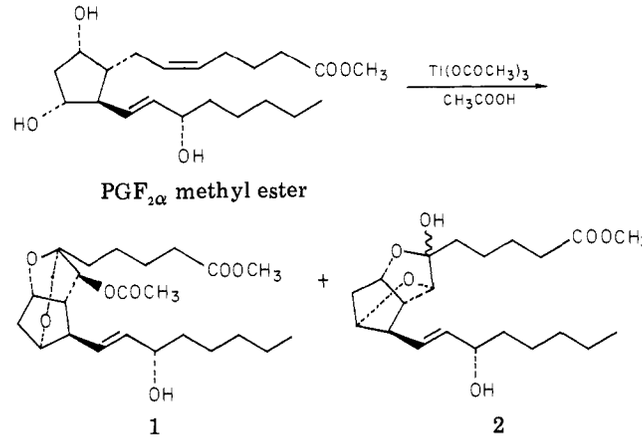
In the case of PGI_2 analogues, the requirement for stabilization of the enol ether moiety constitutes an additional challenge. The most frequently followed approach for this purpose has been to replace the enol ether oxygen by other atoms or groups, such as S, N, and CH_2.[2] Carbaprostacyclin (carbacyclin) seems to be one of the most promising representatives of this line with a substantial stability in water.[3]

Another possible method of designing PGI_2 analogues that are stable to hydrolysis is to insert an electron-withdrawing group adjacent to the enol ether moiety. An example of this kind is Fried's 10,10-difluoro-13-dehydro-PGI_2 with enhanced stability to hydrolysis.[4]

One of the simplest molecules which may be envisaged along this line is 7-oxo-PGI_2 (**9**), where electron density of the enol ether double bond is reduced by the adjacent oxo group.

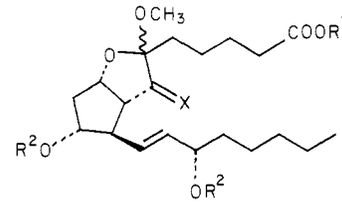
This communication describes the synthesis, stability, and some biological actions of **9**. Preparation of **9** has been hindered by the lack of a suitable method for functionalization of the prostaglandin skeleton at C-7. A first such possibility has emerged in the course of our investigations

Scheme I



of the reaction of $PGF_{2\alpha}$ methyl ester with Tl^{3+} electrophils.[5,6]

According to Scheme I, when $PGF_{2\alpha}$ was reacted with $Tl(OCOCH_3)_3$ in acetic acid, **1** and **2** were formed. Transacetalization of **1** (CH_3OH, BF_3–ether, 25 °C, 1 h) gave an isomeric mixture of diol–methyl acetals **3**.[7] The diol **3** was



3, X = $OCOCH_3$, H; $R^1 = CH_3$; R^2 = H
4, X = $OCOCH_3$, H; $R^1 = CH_3$; $R^2 = Si(CH_3)_2$-*t*-Bu
5, X = OH, H; $R^1 = CH_3$; $R^2 = Si(CH_3)_2$-*t*-Bu
6, X = O; $R^1 = CH_3$; $R^2 = Si(CH_3)_2$-*t*-Bu
7, X = O; $R^1 = CH_3$; R^2 = H

first protected (dimethyl-*tert*-butylsilyl chloride, imidazole, DMF, 40 °C, 5 h)[8] to form **4** in 80% yield: oil; TLC R_f [Kieselgel (Merck); hexane–ethyl acetate, 7:1] 0.42; ^1H NMR ($CDCl_3$) δ 5.52 and 5.38 (dd, vinyls), 4.96 (d, $J_{7,8}$ =

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(7) Experimental details for the preparation of **3** from $PGF_{2\alpha}$ are given in ref 6. The separation of the exo and endo isomers of **3** is not essential, since both methyl acetals form the same olefin, **8**, during the elimination. However the transformation was performed from the major isomer of **3**[6] in order to alleviate characterization of compounds.
(8) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

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Table I. Hemodynamic Changes Produced by PGI_2 and 7-Oxo-PGI_2 Na Salts on Dogs by Intravenous Infusion[a,b]

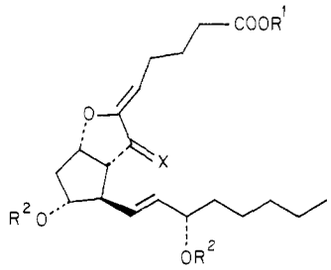
parameters measured	infusion rate, ng kg^{-1} min^{-1}:	hemodynamic change, %			
		7-oxo-PGI_2 Na salt			PGI_2 Na salt
		500	1000	5000	50
blood pressure		−8.1 ± 1.3***	−13.3 ± 3.6*	−49.6 ± 8.0*	−13.6 ± 2.5***
heart rate		0 ± 1.9 (ns)	−2.0 ± 1.9 (ns)	−13.8 ± 4.3*	+3.6 ± 1.1*
cardiac output		−1.6 ± 1.7 (ns)	−3.9 ± 3.4 (ns)	−22.3 ± 10.6*	−5.6 ± 1.4 (ns)
total peripheral resistance		−8.3 ± 1.9***	−13.3 ± 1.9***	−40.7 ± 6.1***	−11.5 ± 3.3*
coronary resistance		−2.2 ± 8.8 (ns)	−6.1 ± 0.6***	−28.8 ± 0.5***	−2.8 ± 4.3 (ns)

[a] Maximum changes occurring during 3 min infusion periods expressed as percent (mean ± SE) of resting values. [b] $n = 4$; ns = nonsignificant; * = $p < 0.05$; ** = $p < 0.02$; *** = $p < 0.001$.

0.5 Hz, C-7 H), 3.65 (s, methyl ester), 3.21 (s, methyl acetal), 2.05 (s, acetyl), 0.88 (*tert*-butyl).

Deacetylation of **4** (methanol, K_2CO_3) afforded the C-7 alcohol **5** in 90% yield: oil; TLC R_f (hexane–ethyl acetate, 4:1) 0.50; ^1H NMR ($CDCl_3$) δ 3.96 (d, $J_{7,8}$ = 0.5 Hz, C-7 H), 5.56, 3.67, 3.18, 0.88. Oxidation of **5** with pyridinium chlorochromate[9] (2 equiv) in CH_2Cl_2 in the presence of $NaOCOCH_3$ gave, after chromatography on silica gel, the ketone **6** as an oil; yield 75%; TLC R_f (hexane–ethyl acetate, 7:1) 0.59; NMR ($CDCl_3$) δ 4.92 (m, C-9 H).[10]

After deprotection of **6** (tetra-*n*-butylammonium fluoride, THF, 25 °C, 1 h, 80%), **7** on heating in HMPA[11] at 150–160 °C for 2 h resulted in the isomerically pure[12] 7-oxo-PGI_2 methyl ester **8**, isolated after column chromatography: oil; yield 47%; TLC R_f (ethyl acetate) 0.44; ^1H NMR ($CDCl_3$) δ 5.6 (m, vinyls), 5.37 (t, C-5 H), 5.06 (m, C-9 H), 3.7 (s, methyl ester). **8** was hydrolyzed ($NaOH–CH_3OH–H_2O$) to give, after acidification to pH 2 with $NaHSO_4$ at 0 °C, 7-oxo-PGI_2 (**9**), which solidified on standing, mp 55–60 °C.



8, X = O; $R^1 = CH_3$; R^2 = H
9, X = O; R^1 = H; R^2 = H
10, X = O; R^1 = Na; R^2 = H
11, X = H, H; R^1 = H; R^2 = H
12, X = H, H; R^1 = Na; R^2 = H

Sodium salt **10** was prepared by equivalent NaOH in water: $[\alpha]^{25}_D$ 80° (*c* 1.0, H_2O). The stability of **10** was studied in water by UV spectroscopy: λ_{max} 289 nm (ϵ 8200). There was no change after 26 days at room temperature in buffers of pH 6.7 and 10.7. Slow decomposition occurred in a buffer of pH 2 ($t_{1/2}$ is about 96 h).

On human platelet-rich plasma against 2 μmol of ADP-induced aggregation, **10** has an IC_{50} value of 15 ng/mL. In the same experiment, an IC_{50} of 1 ng/mL was found for PGI_2 Na salt. According to preliminary results 6 μg/kg of **10** iv has the same disaggregatory action as 2 μg/kg of **12** measured in cats by Gryglewski's "tendon technique".[13,14]

Table II. Activation of Human Platelet Adenylate Cyclase by 7-Oxo-PGI_2 Na Salts[a–c]

compd	concn: 1 μmol	10 μmol
PGI_2 Na salt	374 ± 144*	1740 ± 122***
7-oxo-PGI_2 Na salt	239 ± 118**	825 ± 115**

[a] Data are expressed in percent (mean ± SE) of measurable enzyme activity in the absence of drugs. [b] For method applied see ref 17. [c] $n = 8$; * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$ vs. respective control values.

On the relaxation of the bovine coronary artery, a widely used method for measuring PGI_2-like activity,[15] the following data were obtained (EC_{50} in nanomoles followed by confidence limits for $p = 0.95$ and $n = 6$ in parentheses): 7-oxo-PGI_2 Na salt, 402 (325–479); PGI_2 Na salt, 43 (29–57).

Since no prolongation of the in vivo effect of **10** was experienced by, for example, iv injection (a common finding with previously reported, stable prostacyclin analogues), hemodynamic activity was investigated by infusion in anesthetized, open-chest, mongrel dogs ($n = 4$) surgically prepared for electromagnetic measurements of femoral arterial, left coronary arterial, and ascending aortal blood flows, the latter taken as cardiac output.

Mean peripheral blood pressure was measured in the femoral artery, and drugs were infused into a femoral vein. Heart rate was recorded by a cardiotachometer. Total and coronary vascular resistance were calculated as the ratio of blood pressure to corresponding flows. The data of Table I were obtained by infusing **10** at increasing concentrations, each dose level being infused for 3 min. Maximum changes related to the resting values are expressed in percent. For comparison, data obtained with a single dose of **12** are also given.

10 produces strong activation of membrane adenylate cyclase prepared from human platelet-rich plasma.[16] Comparative data are given in Table II.

In conclusion, 7-oxo-PGI_2 is an analogue of PGI_2 that is stable to hydrolysis. Its pharmacological profile is very similar to and its potency is about one order of magnitude lower than that of the parent compound.

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(10) The most characteristic change in the NMR spectra of **5** and **6**, in addition to the disappearance of the C-7 proton, is the downfield shift of C-9 H from δ 4.67 (**5**) to 4.92 (**6**), due to the carbonyl group.
(11) Shimoji, K.; Konishi, Y.; Arai, Y.; Hayashi, M.; Yamamoto, J. *J. Am. Chem. Soc.* **1978**, *100*, 2547.
(12) Since thermal elimination leads to the more stable enon, the forming double bond must have a *Z* geometry in accordance with the NMR signal of C-5 at δ 5.37 as a triplet.
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2-β-D-Ribofuranosylthiazole-4-carboxamide, a Novel Potential Antitumor Agent for Lung Tumors and Metastases

Sir:

We are currently pursuing 2-β-D-ribofuranosylthiazole-4-carboxamide (NSC 286193, 1) as a high-priority candidate for clinical trials with potential importance for treatment of lung tumors and metastases.

Most patients with bronchogenic carcinoma benefit little from chemotherapy with currently available drugs.[1] Thus, there is a need for the identification of chemotherapeutic agents with greater activity against lung tumors. The murine Lewis lung carcinoma is one of the experimental tumors used by screening programs to identify compounds for development to clinical trial.[2] When used as an iv implant it gives rise preferentially to tumor growth in the lungs with very little involvement of other organs.[3] The ability of a tumor to form colonies in the lung following iv injection is believed to be characteristic of metastic tumors;[4] thus, the iv Lewis lung carcinoma also can be viewed as a model for metastases. We report here that 2-β-D-ribofuranosylthiazole-4-carboxamide (1)[5] has demonstrated remarkable activity against this tumor system.

Compounds prepared as part of a targeted research effort to find new antiviral agents were selected for antitumor screening on the premise that compounds known to exhibit certain kinds of biological activity (e.g., antibiotic, antiviral, antiparasitic) may have an enhanced probability of exhibiting anticancer activity. Compound 1 is an analogue of the potent antiviral agent ribavirin (2),[6-11] which has demonstrated only weak antitumor activity. In contrast, 1 exhibited poor antiviral activity[6,7] but was very effective against several murine tumors, including the Lewis lung carcinoma.

Table I. Effect of 1 on the Life Span of Mice Inoculated Intravenously with Lewis Lung Carcinoma[a]

drug	dose, mg/kg	median life span,[d,e] days post-implant	body wt change[b]	60-day survivors
		Experiment 1		
untreated controls		25.0	1.9	0/40
1	800	11.3	1.3	6/10
	400	9.5	1.2	7/10
	200	ND	1.3	10/10
	100	17	1.3	9/10
	50	ND	2.2	10/10
	25	ND	1.2	10/10
		Experiment 2		
untreated controls		18.4	1.1	0/40
1	800	8.5	−2.1	1/10
	400	ND	0.4	10/10
	200	ND	0.7	10/10
	100	46	1.3	9/10
	50	47	1.6	9/10
	25	ND	1.0	10/10
cyclophosphamide[c]	120	44.0	0.1	4/10
	90	37.5	1.3	5/10
		Experiment 3		
untreated controls		16.9	1.2	0/40
1	800	11.3	−0.8	0/10
	400	20.0	0.5	6/10
	200	16.0	0.7	8/10
	100	ND	0.9	10/10
	50	55	1.2	9/10
	25	47	1.1	7/8
cyclophosphamide[c]	300	16.3	−0.7	2/10
	150	46.0	0.3	4/10
	75	24.5	0.7	1/10
	37	20.4	1.1	0/10
		Experiment 4		
untreated controls		21.1	1.9	0/40
1	25	7	1.5	9/10
	12.5	39.5	1.9	7/10
	6.25	25.3	2.3	0/10
	3.12	22.8	1.8	0/10
	1.56	23.0	1.7	0/10
	0.78	20.0	2.0	0/10

[a] Lewis lung tumor cells (10^6) were implanted iv in groups of 10 BDF_1 mice (experiment 2) or $B6C3F_1$ mice (experiments 1, 3, and 4) (40 mice in untreated control groups) 24 h before initiation of therapy. An aqueous solution of 1 was administered ip on days 1 to 9. Characteristics of the iv model have been described previously.[3] [b] Average body weight in grams on day 5 minus average body weight on day 1. [c] Positive control. Treatment on day 1 only. [d] 60-day survivors are excluded. [e] ND = no deaths.

The activity of 1 against the Lewis lung carcinoma is exceptional for both its degree of activity and its range of effective doses (Table I). Following daily ip administration of an aqueous solution of 1 on days 1-9, an impressive number of 60-day survivors was observed over a wide dosage range in three experiments (Table I, experiments

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