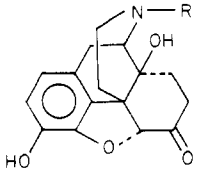
CIMS m/e 415 (M + 1); TLC R_f (silica gel, EtOAc–MeOH–NH_4OH, 98:2:1) 0.50; NMR (CD_3COCD_3) δ 4.45 (d, $J_{5,6}$ = 7.6 Hz, C-5 H), 7.03 and 6.82 (J = 15.4 Hz, vinyls). The base **2** was converted to its HCl salt and crystallized from MeOH–Et_2O (1:1): mp >250 °C; $[\alpha]_D$ −144° (c 0.36, MeOH). Anal. ($C_{22}H_{27}N_2O_6Cl \cdot 0.5MeOH$) C, H, N.

β-FNA (**1**) behaved as a potent reversible agonist with an IC_{50} of 4.8×10^{-9} M when tested on the electrically stimulated guinea pig ileal longitudinal muscle preparation[14] (morphine $IC_{50} = 2.4 \times 10^{-8}$ M). The agonist effect of **1** could be reversed at all incubation times by washing or addition of naltrexone (**7**). However, when the ileum



7, R = CH_2-c-C_3H_5
8, R = CH_3

was incubated with **1** (2×10^{-8} M) for different time periods and then washed (20×), a time-dependent, irreversible narcotic antagonistic effect against morphine was observed (Figure 1). The specificity of the blockage was suggested by the fact that the irreversible effects of **1** could be inhibited by prior addition of the reversible antagonist, naltrexone (**7**; 5×10^{-8} M). Norepinephrine receptors were unaffected by β-FNA treatment.

In view of the generally known chemical properties of Michael acceptors, the SH group is a good candidate for the nucleophile which forms a covalent bond with β-FNA (**1**). This nucleophile has been implicated in other studies on opioid receptors.[15]

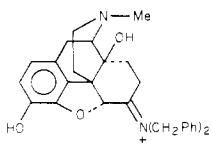
Significantly, when the ileum was treated with **2** (β-FOA) under conditions identical with those for **1**, it produced a reversible agonistic effect ($IC_{50} = 2.7 \times 10^{-8}$ M) but no agonism or morphine antagonism was observed following washing (20×) after 80 min of incubation. The agonistic effect of **2** also was blocked by the irreversible action of **1**.

Since the data suggest that **1** but not **2** forms a covalent bond with opioid receptors, it is likely that the receptor environments which interact with the fumaramate ester moiety of **1** and **2** are different. *This indicates either that 1 and 2 interact differently with a single receptor or that they associate with different receptors, as proposed in the original concept.*[1]

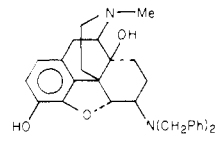
It has been reported[9,10] that both the N-(cyclopropylmethyl) and N-methyl nitrogen mustards, **3** (β-CNA) and **4** (β-COA), form covalent bonds with receptor nucleophiles to afford sustained narcotic antagonism and agonism, respectively, in the guinea pig ileal longitudinal muscle preparation. This is in contrast to the action of the Michael acceptor analogues, where sustained action is observed with the N-(cyclopropylmethyl) compound **1** (β-FNA) but not with its N-methyl counterpart **2** (β-FOA). Since the results of the present study suggest that the receptor environments which interact with the fumaramate ester moieties of **1** and **2** differ, it is likely that a similar difference exists with the nitrogen mustards (**3** and **4**), but is not apparent due to the higher reactivity of the aziridinium ion. Specifically, in contrast to the receptor interaction for the N-(cyclopropylmethyl) compounds, wherein a receptor nucleophile is alkylated by both functionalities, for the N-methyl compounds a less reactive or less accessible nucleophile is readily alkylated by the nitrogen mustard group but not by the Michael acceptor moiety.[16]

Acknowledgment. This research was supported by NIDA Grants DA01533 and DA00289. We thank the capable technical assistance of Miss Joan Naeseth and Mrs. Masako Ikeda.

(13) The amine **6** was obtained stereospecifically in 66% overall yield from **8**. This involved azeotropic removal of H_2O from a mixture of **8** and dibenzylamine (both as benzoate salts) to afford the iminium salt **9**, reduction with $NaCNBH_3$ to the



9



10

dibenzylamino derivative **10**, followed by catalytic hydrogenolysis to **6**. The β configuration at C-6 was confirmed by NMR ($J_{5,6}$ = 6.8 Hz in $CHCl_3$).

(14) H. P. Rang, *Br. J. Pharmacol. Chemother.*, **22**, 356 (1965).

(15) E. J. Simon and J. M. Hiller, *Ann. Rev. Pharmacol. Toxicol.*, **18**, 371 (1978).

(16) This assumes that the N-methyl compounds (**2** and **4**) interact with opioid receptors in an identical fashion but differ in their mode of interaction from the corresponding N-(cyclopropylmethyl) analogues (**1** and **3**) whose binding modes are identical with one another.

(17) The IC_{50} is the concentration of morphine required to inhibit the muscle twitch by 50%.

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10,10-Difluoro-13-dehydroprostacyclin: A Chemically and Metabolically Stabilized Potent Prostacyclin

Sir:

The discovery of prostacyclin, a potent vasodilator and inhibitor of platelet aggregation, by Vane, Moncada, and their collaborators[1] and its isolation and chemical characterization by Johnson et al.[2] represent a milestone in prostaglandin research. Immediately it became apparent that the presence of an unusually acid-labile enol ether grouping[3] seriously impeded the full realization of the therapeutic potential of this substance. As a result, a considerable number of more stable, biologically active analogues have been prepared, mainly by partial synthesis, involving replacement of the ether oxygen by sulfur,[4] ni-

(1) Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R. *Nature (London)* **1976**, *263*, 663.

(2) Johnson, R. A.; Morton, D. R.; Kinner, J. H.; Gorman, R. R.; McGuire, J. C.; Sun, F. F.; Whittaker, N.; Bunting, S.; Salmon, J.; Moncada, S.; Vane, J. R. *Prostaglandins* **1976**, *12*, 915.

(3) (a) Fried, J.; Barton, J. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 2199; (b) Chiang, Y.; Kresge, A. J.; Cho, M. J. *J. Chem. Soc., Chem. Commun.* **1979**, 129.

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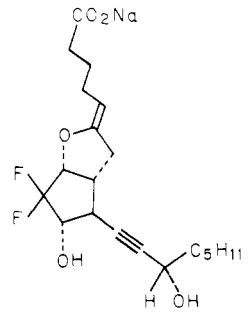
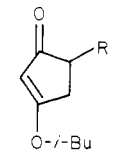
trogen,[5] a methylene group,[6] or manipulation of the 5,6 double bond.[7]

Following the demonstration that introduction of fluorine into biologically active molecules can cause substantial enhancement of biological activity[8] or give rise to enzyme-inhibitory properties,[9] many such examples have been reported, most recently also in the prostaglandin field.[10]

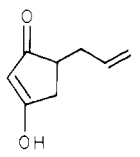
We report the synthesis and some biological properties of 10,10-difluoro-13-dehydroprostacyclin (**1**),[11] in which the



1
1a Me ester



2, R = H
3, R = allyl



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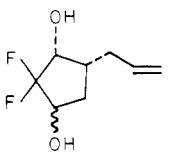
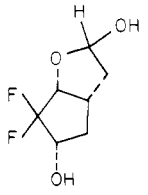


5, α-OH
6, β-OH



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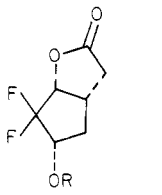
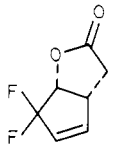


8, R = H
9, R = CF_3SO_2



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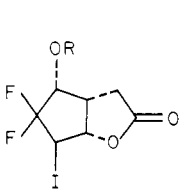
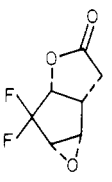


11, R = H
12, R = (−)-MPTA



13

primary purpose for the introduction of fluorine was to increase, by virtue of its electron-withdrawing effect, the stability of the molecule to acid hydrolysis. By happy circumstance this chemical change not only accomplished the purpose in mind but at the same time served to maintain in this substance, both qualitatively and quantitatively, the powerful biological properties of natural prostacyclin. In addition, substitution of the acetylenic group for the 13,14 double bond, designed to block inactivation of **1** by the 15-hydroxyprostaglandin dehydrogenase,[12] did indeed fulfill this purpose.

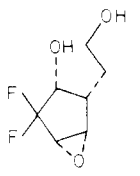
The isobutyl enol ether **2** of cyclopentane-1,3-dione (*i*-BuOH, benzene, *p*-toluenesulfonic acid, 96%) was alkylated[13] (lithium diisopropylamide, allyl iodide at −80 °C in THF) to form **3** in 83% yield. Hydrolysis (1 N HCl at 50 °C, 2 h) afforded the parent dione **4** in 90% yield, which solidified on standing, mp 50–60 °C. Difluorination was accomplished by bubbling $FClO_3$[14] through a solution of **4** in methanol containing 2 equiv of $KHCO_3$ at 20 °C until neutral. The resulting difluoro diketone eluded purification; it was therefore reduced directly with potassium tri-*sec*-butylaluminum hydride[15] in THF, after addition of toluene and careful removal of methanol in vacuo, to yield, after chromatography on silica gel, 36% of the *all-cis*-diol **5** and 15% of a mixture of **5** and the *trans*-diol **6**.[16] Ozonolysis of **5** in methanol at −70 °C [workup with $(CH_3)_2S$] produced the anomeric hemiacetals **7**, which solidified spontaneously, and were immediately oxidized to the lactone **8** with KI_3 in aqueous sodium carbonate at 25 °C in an overall yield of 73% from **5**, mp 76.5–77.5 °C. Dehydration of **8** or its β isomer proceeded via the triflate **9** (trifluoromethylsulfonic anhydride/pyridine, −10 °C → +10 °C, 1.5 h, then 120 °C for 45 min), affording after chromatography the olefin **10** in 78% yield, mp 36–37 °C. This elimination represents the first of a series of reactions in which the strong inductive effect of the *gem*-difluoromethylene group on its neighbor became evident.[17] The tosylate corresponding to **9** was recovered unchanged from boiling pyridine! The new double bond was not sufficiently nucleophilic to be epoxidized efficiently by peracids. The α-epoxide grouping was therefore introduced[18] via the iodolactone **11**. The olefinic lactone **10** was saponified (0.5 N KOH in MeOH, 20 °C, 18 h) and iodolactonized [dry ice to pH 9, I_2 (10 equiv), 25 °C, 18 h] to form **11**, mp 118–119.5 °C, in 93% yield. Base treatment of **11** (1 N KOH in MeOH, 25 °C, 24 h) followed by acidification

(4) Nicolaou, K. C.; Barnette, W. E.; Gasic, G. P.; Magolda, R. L. *J. Am. Chem. Soc.* **1977**, *99*, 7736; Shibasaki, M.; Ikegami, S. *Tetrahedron Lett.* **1978**, 559.
(5) Bundy, G. L.; Baldwin, J. M. *Tetrahedron Lett.* **1978**, 1371.
(6) Kojima, K.; Sakai, K. *Tetrahedron Lett.* **1978**, 3743; Nicolaou, K. C.; Sipio, W. J.; Magolda, R. L.; Seitz, S.; Barnette, W. E. *J. Chem. Soc., Chem. Commun.* **1978**, 1067; Morton, D. R., Jr.; Brokaw, F. C. *J. Org. Chem.* **1979**, *44*, 2880; Shibasaki, M.; Ueda, J.; Ikegami, S. *Tetrahedron Lett.* **1979**, 433; Sugie, A.; Shimomura, H.; Katsube, J.; Yamamoto, H. *Tetrahedron Lett.* **1979**, 2607.
(7) Ohno, K.; Nishiyama, H. *Tetrahedron Lett.* **1979**, 3003, 3481.
(8) Fried, J.; Sabo, E. F. *J. Am. Chem. Soc.* **1954**, *76*, 1455; Fried, J.; Abraham, N. A. *Org. React. Steroid Chem.* **1972**, *1*, 423.
(9) Heidelberger, C.; Chaudhuri, N. K.; Danneberg, P.; Mooren, D.; Griesbach, R.; Duschinsky, R.; Schnitzer, R. J.; Pleven, E.; Scheiner, J. *Nature (London)* **1957**, *179*, 663.
(10) Grieco, P. A.; Sugahara, T.; Yokoyama, Y.; Williams, E. *J. Org. Chem.* **1979**, *44*, 2189. Grieco, P. A.; Williams, E.; Sugahara, T. *Ibid.* **1979**, *44*, 2194, and earlier references cited therein.
(11) Structural formulas **1** and **15–23** are intended to represent 1:1 mixtures of the structures shown and the diastereomeric structures in which the centers at 8, 9, 11, and 12 are of opposite chirality. All new compounds were characterized by ^1H and ^{19}F NMR, IR, and mass spectra, as well as elemental analyses.
(12) Jarabak, J.; Braithwaite, S. S. *Arch. Biochem. Biophys.* **1976**, *177*, 245.
(13) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.
(14) $FClO_3$ was purified by passage through 2 N NaOH, 5% $Na_2S_2O_3$, and methanol (to saturate vapor). Excess $FClO_3$ was removed with N_2 prior to workup. With this precaution and working at 20–25 °C, $FClO_3$ proved a safe reagent.
(15) Potassium tri-*sec*-butylaluminum hydride reduction produced stereoselectively only the *cis*-1-hydroxy-2-allyl compounds **5** and **6**, whereas borohydride furnished all four possible isomers, which were isolated in pure form. The stereochemistry of all four isomers was established with the aid of ^{19}F NMR spectroscopy. 2,2-Difluoro-1,3-*cis*-cyclopentanediols exhibit two fluorine signals separated by 19 to 20 ppm, unperturbed by the presence of substituents in the 4 and 5 positions. As expected, the corresponding *trans*-diols show but one fluorine signal.
(16) The separation of **5** and **6** is not essential, since both alcohols form a single olefin on elimination. In fact, the subsequent reactions were carried out independently with **5** and **6** and with mixtures of the two epimers.
(17) Other reactions so effected were the iodolactonization, the formation of the epoxide, which required strong base for an extended period of time, the alane reaction which regioselectively furnished a single hydroxyacetylene, and the formation of the iodo ether which rquired an excess of I_2 for an extended period of time.
(18) Corey, E. J.; Noyori, R. *Tetrahedron Lett.* **1970**, 311.

effected only partial lactonization of the intermediate epoxy acid, which was completed by methylation with CH_2N_2 and allowing the methyl ester to remain on a silica gel column for 24 h prior to elution: yield of **13** 74%; mp 92–92.5 °C.

The olefin **10** and the iodolactone **11** were resolved independently. The hydroxy acid derived from **10** (0.1 N KOH, oxalic acid to pH 2, extraction) was treated with (+)-α-(1-naphthyl)ethylamine, the resulting salt was crystallized from ethyl acetate in 39% yield [mp 161–162 °C; $[\alpha]_D$ (CH_3OH) −45.3°] and decomposed with base, and the amine was removed by extraction. Iodolactonization (vide supra) furnished (+)-**11**: $[\alpha]_D$ (CH_3OH) +78.0°; mp 146 °C (softens at 136 °C). The absolute configuration of (+)-**11** was determined by the Horeau[19] and Mosher[20] methods, both of which predict the absolute configuration of (+)-**11** to be opposite of that shown.[21] The esterification of **11** with optically active α-methoxy-α-trifluoromethylphenylacetic acid (MTPA),[22] which forms the basis of the Mosher method, may also serve for the resolution of **11**. The esters derived from (*S*)-(−)-MTPA (**12** and its diastereomer) were separated by high-pressure LC using silica gel, and their purity was ascertained by proton NMR.[23] The separated esters were then converted into the enantiomeric epoxy lactones **13** and *ent*-**13** as described above. The faster moving ester **12** [mp 108–110 °C; $[\alpha]_D$ ($CHCl_3$) −6.4°] furnished (+)-**13** [mp 110.5–111 °C; $[\alpha]_D$ ($CHCl_3$) +102°] of natural configuration, while the slower moving amorphous ester ($[\alpha]_D$ ($CHCl_3$) −5.9°) furnished its enantiomer.

The synthesis was continued with the racemic epoxy lactone **13**, which was reduced to the diol **14** ($LiAlH_4$, −40 °C, 3 h) in 87% yield, mp 50–50.5 °C, and the latter reacted with dimethyl-(3*S*)-*tert*-butyloxy-1-octynylalane in toluene–hexane at 55 °C for 3 h.[24,25] The resulting triol **15** (71% yield) and all subsequent products represent 1:1 mixtures of diastereomers[11] which could not be separated. This mixture was employed in the final steps of the synthesis. Oxidation of **15** (Pt, O_2, acetone/H_2O)[24] yielded 75% of the lactone **16**, which was reduced (*i*-Bu_2AlH in hexane/toluene, −70 °C)[24] to the hemiacetals **17** in 91% yield. Wittig reaction [$Ph_3P{=}CH(CH_2)_3CO_2Na$, 6 equiv, 1 h, 25 °C] afforded 77% of the *tert*-butyl ether **18**, which was debutylated (trifluoroacetic acid/anisole, 2 h, 0 °C, then Na_2CO_3) to form 10,10-difluoro-13-dehydro-$PGF_{2\alpha}$ (**19**) in 84% yield.[24] The methyl ester of **19** (CH_2N_2 in ether/CH_3OH) was converted into the iodo ether **20** ($NaHCO_3$, I_2 in ether, 5 equiv, 3.5 h, 0 °C)[26,27] in 81% yield, and the latter was dehydrohalogenated (6 equiv of DBU, toluene, 90 °C, 0.5 h) to form 10,10-difluoro-13-dehydroprostacyclin methyl ester (**1a**; 78%) and its Δ^4-isomer **21** (12%), which were separated by TLC. Both **1a** and **21** were converted into their sodium salts (0.4 N NaOH, 2 h, 25 °C) **1** and **22**, respectively.



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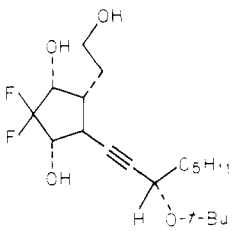

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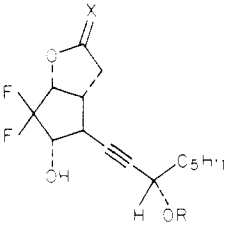
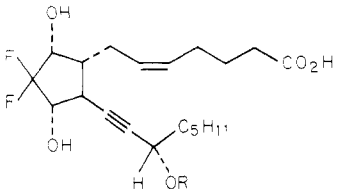
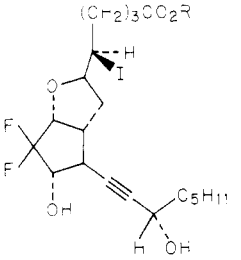


16, X = =O
17, X = <OH H



18, R = *t*-Bu
19, R = H



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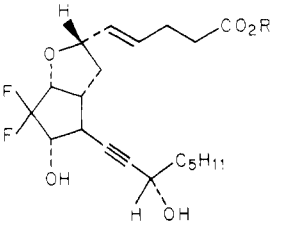
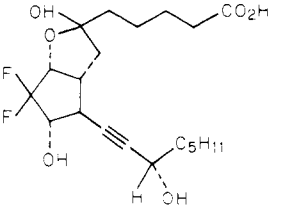


21, R = CH_3
22, R = Na

The greatly enhanced stability of **1** in acid media compared to that of PGI_2 was readily apparent when solutions of **1** and PGI_2 sodium salt were acidified with oxalic acid to pH 3, extracted with ether at 0 °C, and the recovered acids methylated with CH_2N_2. TLC of the material derived from the difluoro compound **1** yielded mainly its methyl ester **1a**[28] and only a faint spot for 10,10-difluoro-13-dehydro-6-keto-$PGF_{1\alpha}$ (**23**), while in the parallel



23

experiment with PGI_2 methyl ester, 6-keto-$PGF_{1\alpha}$ methyl

(19) Horeau, A. *Tetrahedron Lett.* **1961**, 506; Horeau, A.; Kagan, H. B. *Tetrahedron* **1964**, *20*, 2431; Mabry, T. J.; Renold, W.; Miller, H. E.; Kagan, H. B. *J. Org. Chem.* **1966**, *31*, 681.

(20) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143.

(21) This prediction is based on the assumption that CF_2 is the smaller of the two groups flanking the carbinol. It does not take into consideration the electronic nature of the CF_2 group, the influence of which has not been sufficiently assessed in the literature.

(22) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1966**, *34*, 2543. The rate of acylation was substantially increased by the use of 4-(dimethylamino)pyridine as a catalyst. Cf. Steglich, W.; Hofle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981.

(23) The slower moving (−)-MTPA (+)-iodolactone ester (EtOAc/hexane, 1:1) shows CH_2 protons at δ 2.47 (dd, J = 18.9 and 3.6 Hz) and 2.64 (ddd, J = 19.5, 11.6, and 2.0 Hz), while the faster moving (−)-MTPA (−)-iodolactone ester shows CH_2 protons at δ 2.26 (dd, J = 18.5 and 3.5 Hz) and 2.48 (dd, J = 18.9 and 11.7 Hz).

(24) Fried, J.; Lin, C. H.; Sih, J. C.; Dalven, P.; Cooper, G. F. *J. Am. Chem. Soc.* **1972**, *94*, 4342, 4343.

(25) The epoxide opening reaction was completely regiospecific under these conditions. Cf. Fried, J.; Sih, J. C. *Tetrahedron Lett.* **1973**, 3899.

(26) Whittaker, N. *Tetrahedron Lett.* **1977**, 2805.

(27) Although the iodo ether **20** showed a single spot on TLC, it probably represents a mixture of the structure shown and the other possible isomer formed by trans addition to the 5,6 double bond, in the approximate ratio of 7:1 as demonstrated by the results of the elimination with DBU.

(28) In contrast to PGI_2 methyl ester which could not be isolated unchanged from silica gel plates, **1a** was recovered quantitatively even after prolonged exposure.

ester was the sole product. Pure **23** was obtained by hydrolysis with 0.01 N HCl in THF at 25 °C for 15 min.

The half-life of **1** was determined by incubating a 10^{-8} M solution in Krebs bicarbonate buffer saturated with CO_2 (pH 7.4) at 37 °C and measuring the capacity of this solution at 4-h intervals to cause relaxation of renal mesenteric artery previously contracted by $PGF_{2\alpha}$. After 24 h, relaxation had decreased by 50%, while PGI_2 under identical conditions required only 10 min.[29] In these experiments, **1** and PGI_2 showed EC_{50} values of $2.3 \pm 0.5 \times 10^{-9}$ and $3.3 \pm 0.5 \times 10^{-9}$ M, respectively.[30] Relaxation of bovine coronary artery is uniquely characteristic for PGI_2 among all the prostaglandins.[31] In this assay, **1** and PGI_2 showed $EC_{50} = 8.5 \pm 1.6 \times 10^{-9}$ and $2.8 \pm 0.6 \times 10^{-8}$, respectively.[29] Comparison of the potency of **1** and PGI_2 in causing complete inhibition of ADP and arachidonic acid induced aggregation of human platelets showed **1** ($ED_{100} = 10^{-8}$ M) to be 70% as active as PGI_2.[1,32]

Intravenous administration of **1** and PGI_2 in doses of 1 to 2×10^{-8} mol/kg as a bolus to an anesthetized dog showed the difluoro derivative to be equal in potency to the natural product in lowering blood pressure and decreasing peripheral and increasing renal blood flow.[33] Only at the highest levels of **1** was a two- to threefold prolongation of action observed when **1** was compared with equipotent levels of PGI_2. Since **1** was shown to be completely resistant to 15-hydroxyprostaglandin dehydrogenase,[34] rapid excretion either unchanged or after β- and/or P-450 catalyzed oxidation is probable.

10,10-Difluoro-13-dehydro-$PGF_{2\alpha}$ (**19**) possesses luteolytic activity equal to that of $PGF_{2\alpha}$ in a hamster antifertility assay.[35]

In summary, the total synthesis of the prostacyclin analogue **1** is described, which mimicks natural PGI_2 in all respects so far examined, except for its 150 times greater half-life and its failure to be inactivated by the 15-hydroxyprostaglandin dehydrogenase.

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(30) The material prepared and tested in this work represents a 1:1 mixture of diastereomers consisting of structure **1** and its ent-15-epi derivative. To assess the potency of the latter, we prepared and examined its nonfluorinated analogue for its effect on the renal mesenteric artery. In contrast to **1**, this substance caused *contraction* at the 10^{-6} M level, too high to substantially influence the effects of **1**. Our potency estimates are therefore reported in terms of a 50% content of **1**.
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(34) Jarabak, J. Department of Medicine, University of Chicago, unpublished results.
(35) Performed through the courtesy of the National Institute for Child Health and Development.

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5-Substituted 2-Amino-6-phenyl-4(3*H*)-pyrimidinones. Antiviral- and Interferon-Inducing Agents

Sir:

A survey of the variety of agents capable of stimulating interferon (IF) production demonstrates that most range in size from viruses and bacterial cell walls to synthetic or biopolymers [e.g., dextran and poly(I:C)].[1] However, there is also a small group of low-molecular-weight compounds which induce IF. Included among these compounds which have been reported to induce IF either in vivo or in vitro are diamines such as *N,N*-dioctadecyl-*N',N'*-bis(2-hydroxyethyl)propanediamine,[2] *N,N'*-dihexadecyl-*m*-xylylenediamine,[3] bis(diethylamino)fluorenone (tilorone),[4] several acridines represented by quinacrine,[5] a 1,5-bis[[(diethylamino)ethyl]amino]-9,10-anthraquinone,[6] 4-[[3-(dimethylamino)propyl]amino]-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]quinoline,[7] and such inhibitors of cellular proliferation as cycloheximide, actinomycin D, and 5,6-dichloro-1-(β-D-ribofuranosyl)benzimidazole.[8,9] Also part of this class of IF inducers is the recently reported 2-amino-5-bromo-6-methyl-4(3*H*)-pyrimidinone (**II**, R_1 = Br; $R_2 = CH_3$).[10] We wish to report that the corresponding 6-phenylpyrimidinones (**II**, $R_2 = C_6H_5$) exhibit substantially enhanced IF induction and antiviral activity.[11]

The synthesis of the pyrimidinones of interest proceeds from the requisite β-keto ester (**I**), itself available in a one-step acylation of the dianion of monoethyl malonate (Scheme I).[12] Condensation of the β-keto ester with guanidine afforded the 2-amino-6-phenyl-4(3*H*)-pyrimidinones (**II**) in 50–70% overall yield.

The 5-halogen-substituted analogues were prepared from **II**, R_1 = H, by halogenation in acetic acid for chlorination (*N*-chlorosuccinimide) and bromination (*N*-bromosuccinimide or Br_2) or in a basic, mixed solvent system ($CHCl_3$, 1 N NaOH, I_2) for iodination (60–90% yield).[13] Halogenation could also be carried out by heating in DMF with

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