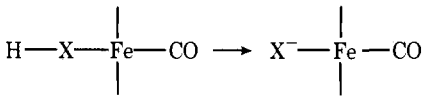
A comparison of the spectra of heme complexes of oxygen and nitrogen anions with those of the biologically important sulfur anions reveals some interesting trends. Thus deprotonation of proximal bases in the carbon monoxide complexes



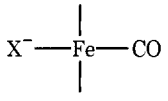
leads to red shifts in the Soret band of 414 → 438 for X = $^-$OR, 420 → 430 for X = imidazolate, compared with 420 → 460 for X = RS$^-$.[9] The deoxy forms of the RO$^-$ and imidazolate complexes also display a rather large red shift compared with complexes of their conjugate acids, e.g., 423 → 429 for the diimiazolate heme complex and 430 to 440 for the 2-methylimidazolate complex.

The reactivity of heme complexes of nitrogen and oxygen proximal bases is also greatly altered by deprotonation, an effect also seen in the RS$^-$–heme complexes.[9] We find that the diimidazolate heme (at 0.1 M imidazole concentration) has a pressure for carbon monoxide half-saturation ($P_{1/2}^{CO}$) of ~0.3 Torr compared with ~0.004 Torr for a similar solution of diimidazole–protoheme complex, both in $CetMe_3NBr$ suspension,[14] and ~18 Torr for an RS$^-$–heme complex in dimethylacetamide[11] or in $CetMe_3NBr$ suspension.[13b]

These results suggest that *red-shifted Soret bands* and *lowered CO affinities,* formerly observed for RS$^-$ complexes, are general properties of *heme–anion complexes.*

Comparisons of these spectra with those of hemoproteins affords some conclusions and suggests some speculations concerning deprotonation of proximal bases as a general phenomenon in hemoproteins.[4] The typical deoxy and carbonmonoxy bands for RO$^-$ complexes at 444 and 438 nm, respectively, are not observed in hemoproteins, making it unlikely that serine or tyrosine anions are proximal iron ligands.[15] This leaves mercaptide as the only ligand which gives the spectra recorded for cytochrome P-450. However, the 440, 560, and 595 bands for the 2-methylimidazolate complex and 430, 545, and 575 for its CO complex compare well with the 440, 560, and 595 bands and 424, 542, and 573 bands of deoxy and CO complexes of peroxidases[16,17] and catalase[18] and are quite different from those of hemoglobin or its chelated protoheme model.[13]

The suggestion of Peisach[4] and of Morrison and Schonbaum[5] that deprotonation or strong hydrogen bonding of the proximal imidazole constitutes a means of controlling hemoprotein reactivity seems to be supported by these data. This conclusion is further strengthened by our finding that heme-anion complexes are much more sensitive to oxidation by dioxygen than are their neutral complexes, just as peroxidases[16-18] and cytochrome P-450[19] are more easily oxidized by dioxygen than are hemoglobin or myoglobin. Additionally, the low affinity of the heme–anion complexes for CO is shared by peroxidases and P-450.



Further comparisons of heme–anion complexes with hemoproteins by other physical and chemical methods are in progress to test these speculations.[20]

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(1) This research was supported by the National Science Foundation, Grant CHE 75-22283.
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(14) The difference is less in Me_2SO, which competes to reduce CO affinity. The imidazolate–heme complex was prepared in $CetMe_3NBr$ by titrating the imidazole complex with sodium hydroxide. At hydroxide ion concentration (>0.2 M) sufficient to deprotonate the iron-bound imidazole, hydroxide begins to compete for the heme as indicated by traces of the band at 595 nm like that in entry 3.
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(20) NOTE ADDED IN PROOF. The reduction in CO stretching frequency upon imidazole deprotonation (1951 → 1935 cm^{-1} in Me_2SO) is also consistent with these suggestions.

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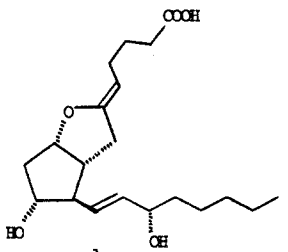
6,9-Pyridazaprostacyclin and Derivatives: the First "Aromatic" Prostacyclins[1]

Sir:

Prostacyclin (PGI_2, **1**),[2] owing to its remarkable biological properties and its chemical instability, has prompted an intense search for biological mimics with improved properties as potential therapeutic agents.[3] One possible solution to the



1

problem of retaining biological activity and increasing stability at the same time is to substitute the second ring of prostacyclin with an aromatic nucleus. This concept of the "aromatic" prostacyclins retains the sp^2 character of C-6, a seemingly important feature for biological activity,[4] and, therefore, appeared to be an attractive proposition. In order to test this hypothesis we initiated a program directed toward the synthesis of such molecules and in this communication we report the synthesis of the first aromatic prostacyclin, namely 6,9-pyridazaprostacyclin (**16**), and its derivatives, dihydropyridazaprostacyclin (**14**) and *N*-oxides **18a** and **18b**, and describe our findings on their biological and chemical properties.

Model studies with the diketone **2** indicated that the desired bicyclic pyridaza system **3** could be constructed quite efficiently and under very mild conditions by the action of hydrazine in ethanol, THF, or aqueous THF followed by treatment with PtO_2. This methodology led to the isolation of **3**[5] in

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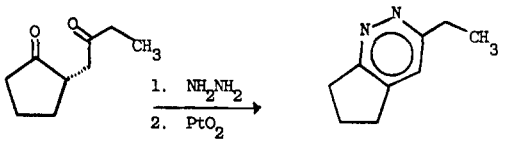
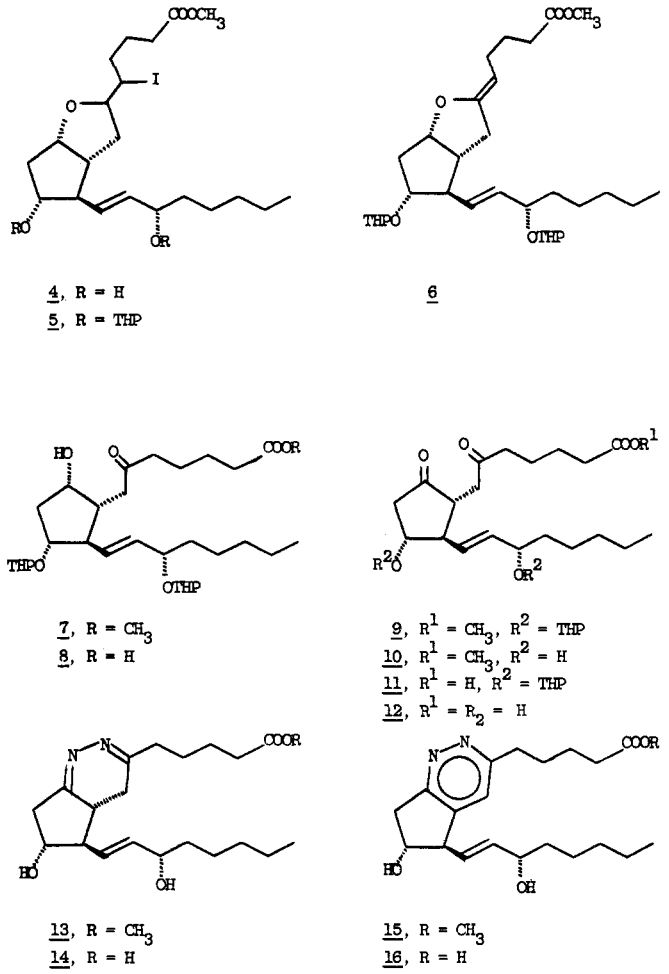


2 3

90% yield as a stable oil. 3,6-Dimethylpyridazine was similarly obtained from acetonylacetone in 80% yield. This new methodology for the synthesis of pyridazines from 1,4-dicarbonyl compounds was found to be unique[6] for the construction of the rather complex pyridazaprostacyclins and is expected to find further useful applications in other sensitive cases.

The requisite prostanoid diketones **10** and **12** for the construction of the pyridazaprostacyclins **15** and **16,** respectively, were obtained from the iodide **4**[9] as follows. Protection of **4** as the (bis)tetrahydropyranyl ether **5** (dihydropyran, *p*-toluenesulfonic acid, CH_2Cl_2, 25 °C), followed by treatment with excess DBU in toluene solution at 110 °C, led to the prostacyclin derivative **6** in high yield. Traces of acetic acid in wet THF (25 °C) led to 11,15-bis(THP)-6-keto $PGF_{1\alpha}$ methyl ester **7** in 78% overall yield from **4**. Oxidation of **7** with pyridinium chlorochromate (CH_2Cl_2, 25 °C) or Jones reagent (acetone, −20 °C) led to the diketone **9** (76% yield) which upon deprotection with AcOH-THF-H_2O (3:2:2) at 45 °C furnished 6-keto PGE_1 methyl ester **10** (80%). Attempts to hydrolyze this ester to the acid **12** under aqueous base conditions were unsuccessful apparently because of the sensitive ketone functions. The acid **12** was, therefore, prepared from **7** in 65% overall yield by the sequence (i) hydrolysis of the ester with LiOH in aqueous methanol at 25 °C, (ii) Jones oxidation in acetone at −20 °C, and (iii) removal of the tetrahydropyran groups as above.



4, R = H
5, R = THP

6

7, R = CH_3
8, R = H

9, R^1 = CH_3, R^2 = THP
10, R^1 = CH_3, R^2 = H
11, R^1 = H, R^2 = THP
12, R^1 = R_2 = H

13, R = CH_3
14, R = H

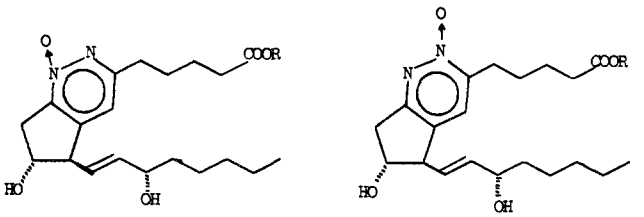
15, R = CH_3
16, R = H

3

Treatment of the diketone methyl ester **10** with hydrazine (1.0 equiv, 95+%) in THF-H_2O (9:1) at 25 °C for 5 min led to a new compound (R_f 0.22, silica-10% CH_3OH in CH_2Cl_2) which was directly oxidized by stirring over PtO_2 to afford 6,9-pyridazaprostacyclin methyl ester (**15**)[10] isolated by careful preparative layer chromatography to avoid decomposition (R_f 0.24, silica-10% CH_3OH in CH_2Cl_2,60% from **10**). The acid **16** could not be prepared from **15** by aqueous base hydrolysis owing to the base sensitivity of the compound and, therefore, it was prepared directly from 6-keto-PGE_1 (**12**) and hydrazine by the sequence described above.

The formation of the pyridaza compounds **15** and **16** presumably proceeds by oxidation of the initially formed diimino compounds **13** and **14,** respectively (or/and their dihydraza tautomers). While all four compounds (**13–16**) were found to be stable in solution, some decomposition occurred upon concentration, particularly with **13** and **14** which could not be purified chromatographically using conventional methods. Slow destruction was also observed with **15** and **16,** although purification could be achieved in the case of **15** by rapid and careful chromatographic procedures.

Oxidation of crude **15** (1.2 equiv of *m*-CPBA, CH_2Cl_2, 25 °C) led to a mixture of the two *N*-oxides **17a,b** purified chromatographically but not separated (R_f 0.28, silica-10% CH_3OH in CH_2Cl_2) (~1:1 by ^1H NMR)[10] in 60% overall yield from **10.** The acids **18a,b** were similarly obtained from **16** and purified chromatographically (R_f 0.34, silica-20% CH_3OH in CH_2Cl_2) (~1:1 ratio by ^1H NMR, 60% total yield from **12**). Methylation (CH_2N_2) of **18a,b** led to the esters **17a,b.** All four compounds (**17a,b, 18a,b**) were stable in solution or neat under neutral conditions, although basic media led to extensive destruction. It is possible that the observed relative instability of **15** and **16** arises from their self-promoting tendency to eliminate H_2O due to their basic nature, whereas removal of the basic character by oxidation to the *N*-oxides leads to enhanced stability.



17a, R = CH_3
18a, R = H

17b, R = CH_3
18b, R = H

4

Preliminary biological investigations indicate interesting biological properties for a number of the reported compounds. Thus, for example, compounds **12, 14,**[12] and **16** showed potent inhibition of human blood platelet aggregation[13] and dilatory properties on the isolated perfused cat coronary artery.[13] The ready availability and properties of these compounds should facilitate[13] research and open new directions in this biologically important area of research. Full biological data will be published elsewhere.[14]

References and Notes

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(10) ^{1}H NMR (220 MHz, $CDCl_3$): **15**, τ 3.03 (s, 1 H, H-7), 4.36 (m, 2 H, H-13, H-14); **17a,b**, τ 2.68 (s, 0.5, H-7 meta to *N*-oxide),[11] 3.20 (s, 0.5 H, H-7 para to *N*-oxide),[11] 4.28 (m, 2 H, H-13, H-14).
(11) A. G. Moritz and D. B. Paul, *Aust. J. Chem.*, **22**, 1305 (1969).
(12) 6,9-Pyridazaprostacyclin showed higher potency than PGE_1 but less than PGI_2 in inhibiting platelet aggregation and dilating the isolated perfused cat coronary artery.[13]
(13) Tests on platelet aggregation were carried out in Professor J. B. Smith's laboratories at the Cardeza Foundation, Thomas Jefferson University, Philadelphia, Pa. 19107. The biological studies with the cat coronary artery were performed in Professor A. M. Lefer's laboratories, Department of Physiology, Thomas Jefferson University, Philadelphia, Pa. 19107.
(14) This research was supported by the National Institutes of Health (Heart, Lung and Blood Institutes, HV-E2931) and Merck Sharp & Dohme, U.S.A., and Ono Pharmaceutical, Japan. ^{1}H NMR spectra were obtained at the Middle Atlantic Regional NMR Facility (NIH No. RR542) at the University of Pennsylvania directed by Dr. G. McDonald.

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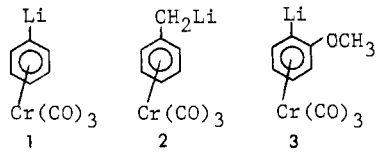
Metalation of Arenechromium Tricarbonyl Complexes and Electrophilic Trapping of the Complexed Phenyllithium Intermediate

Sir:

Proton abstraction from aromatic rings by strong base (metalation) is a method of direct activation of a ring carbon atom as a nucleophile.[1] Simple arenes can be metalated under special conditions,[1,2] but alkylarenes undergo preferential side-chain metalation (benzylic carbanion).[3] Recent developments suggest that functionalized arenes can allow efficient, selective, and preparatively useful metalation ortho to the functional group.[1c,4]

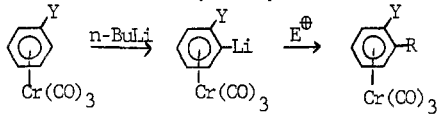
The chromium tricarbonyl unit forms π complexes with arenes, and perturbs the reactivity of the arene ligand in several distinct ways,[5] including enhanced acidity of benzylic C–H bonds[6] and the arene ring C–H bonds.[7] Preliminary observations suggest that π-(benzene)chromium tricarbonyl and bis(benzene)chromium can be directly metalated with alkyllithium reagents in low yield.[7b-d] We have been interested in



1 2 3

generating intermediates such as **1** and **2**, because subsequent reaction with carbon electrophiles would produce directly π-arenechromium tricarbonyl complexes with elaborated substituents, useful in further nucleophilic substitution via the addition/oxidation method.[8,9]

Table I. Electrophilic Quenching of the *o*-Lithio π-(Arene)chromium Tricarbonyl Complexes



(1)

entry	group Y	group E^+	product, % yield[a] (% recovered starting material)
1	H	CO_2	$-CO_2CH_3$,[b] 72 (0)
2	H	CH_3COCH_3	$-CH(OH)(CH_3)_2$, 29 (60)
3	H	CH_3OSO_2F	$-CH_3$,[c] 91 (2)
4	H	PhCHO	$-CH(OH)Ph$, 60 (0)
5	H	$(CH_3)_3SiCl$	$-Si(CH_3)_3$, 94 (0)
6	H	I_2	$-I$,[d] 76 (<5)
7	OCH_3	CH_3OSO_2F	$-CH_3$,[c] 65 (5)
8	OCH_3	CO_2	$-CO_2CH_3$,[b] 86 (0)
9	OCH_3	CH_3COCH_3	$-C(OH)(CH_3)_2$, 85 (<10)
10	OCH_3	PhCHO	$-CH(OH)Ph$,[e] 94 (0)
11	OCH_3	$(CH_3)_3SiCl$	$-Si(CH_3)_3$,[f] 70 (0)
12	F	CH_3OSO_2F	$-CH_3$,[c] 68 (30)
13	F	CO_2	$-CO_2CH_3$,[b] 99 (0)
14	F	CH_3COCH_3	$-C(OH)(CH_3)_2$, 85 (15)
15	F	PhCHO	$-CH(OH)Ph$,[e] 57 (0)
16	F	$(CH_3)_3SiCl$	$-Si(CH_3)_3$,[f] 46 (0)
17	Cl	CH_3OSO_2F	$-CH_3$,[c] 81 (6)
18	Cl	CO_2	$-CO_2CH_3$,[b] 98 (0)
19	Cl	CH_3COCH_3	$-C(OH)(CH_3)_2$, 67 (28)
20	Cl	PhCHO	$-CH(OH)Ph$,[e] 71 (0)
21	Cl	$(CH_3)_3SiCl$	$-Si(CH_3)_3$,[f] 49 (0)

[a] Unless otherwise noted, the chromium complexes were crystallized and fully characterized with ^{1}H NMR and combustion analysis. [b] The methyl ester complex was obtained by treatment of an ethereal solution of the crude carboxylic acid with diazomethane. [c] This yield was determined by GLC analysis of the free arenes after oxidative decomplexation (ceric ammonium nitrate, 25 °C). [d] The product containing π-(benzene)chromium tricarbonyl (<5%) which is difficult to remove efficiently. Recrystallization provides pure product, 54% yield. [e] The product was a mixture of diastereoisomers; the yield is for the mixture. [f] The 2,6-disilylated product was observed, 10–20% yield.

The investigation in our laboratory began with the observation that, while *tert*-butyllithium added to the π system of the arene ligand,[9,10] *n*-butyllithium acted as a base, producing a species (presumably **1**) which reacted with excess iodine to give iodobenzene (71% yield). Under optimum conditions (*n*-butyllithium, THF, tetramethylethylenediamine, −78 °C, 0.3 h), **1** was formed with high efficiency and could be trapped by addition of 1 mol equiv of iodine and other electrophiles (Table I). Under these conditions, the arene–chromium bond is maintained (eq 1). Complex **1** showed a contrast with phenyllithium in reaction with acetone; addition to the carbonyl group was a minor process (29%), while proton abstraction from the acetone accounted for 60% of the material.[11] In general, the ligand can be detached from the chromium in high yield by treatment with excess iodine or with cerium(IV) at 25 °C.[9]

Treatment of π-(anisole)chromium tricarbonyl[12] with *n*-butyllithium (ether, −35 °C, 0.5 h) produced a yellow solution of **3**, which is stable for many hours at −20 °C, but decomposes slowly at higher temperature. Entries 7–11 (Table I) display the results of reaction with representative electrophiles. Acetone reacted by addition to the carbonyl group. With methylating agents such as methyl iodide (instead of methyl fluorosulfonate, entry 7), three products are detected after removing the chromium: anisole (25%), *o*-methylanisole (30%), and 2,6-dimethylanisole (30%). This mixture is consistent with rapid proton transfer during methylation.[13] Attempts to alkylate **3** with simple primary alkyl sulfonate esters failed. However, overall alkylation can be achieved in good yield by

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