derivative **5** in pure form after column chromatography on silica gel; IR (liquid film) 2560 cm^{-1} (SH). The endodisulfide unit in **6** could be prepared under carefully chosen conditions which precluded further oxidation and other side reactions.[5] Specifically, upon treatment of **5** with 1.5 equiv of active manganese dioxide in degassed toluene at −20 °C for 40 min under argon,[6] **6** was formed along with minimal side products, and could be isolated in 86% yield after column chromatography on silica gel using cyclohexane-ethyl acetate (4:1) as eluent. Removal of the tetrahydropyranyl ether from disulfide **6** (acetic acid-water-tetrahydrofuran, 12:3:2) at 40 °C for 1 h afforded the disulfide analogue of PGH_2 (**1**) in 49% isolated yield; $[\alpha]^{18}_D$ +3.6° (*c* 0.6, chloroform).[7] The structural assignment follows from (a) the mass spectrum (molecular ion at *m/e* 398.1959, calcd 398.1949); (b) the IR spectrum; and (c) a negative Ellman test[8] on TLC assay.[9]

Further support regarding the stereochemistry of product **1** was obtained by the chemical synthesis of the 9,11-epimer of **1.** Thus, starting from the 15-tetrahydropyranyl ether of $PGF_{2\alpha}$ methyl ester[10] and using the same procedure used for the sequence, **2** to **1,** there was produced 9β,11β-dithio analogue **7.** Although disulfides **1** and **7** are spectroscopically indistinguishable (IR and NMR), the thin layer chromatographic behavior of **7** on silica gel using cyclohexane-ethyl acetate as eluent is different from that of compound **1:** R_f 0.35 for **1** and 0.33 for **7.** In addition, **1** was very active biologically as an endoperoxide mimic whereas the epimer, **7,** was not.

Like the endoperoxides, cyclic sulfide **1** is very effective in contracting the aorta strips.[11] Thus, analogue **1** was 24 times more active than PGH_2 and 5000 times more active than PGE_2 in this assay. Endodisulfide **1** also caused marked, rapid and irreversible aggregation of platelets washed in Tyrodes solution.[12] Further study of the biological activity of **1** is in progress.[13]

The simple and effective synthesis of endodisulfide **1** described above makes available a biologically active member of the PGH_2 analogue series which, in contrast to the highly labile PGH_2, does not undergo facile decomposition chemically[14] and may not be rapidly metabolized in vivo.[15]

Acknowledgment. The authors wish to thank Dr. Hisashi Yamamoto of Kyoto University for important and stimulating discussions.

References and Notes

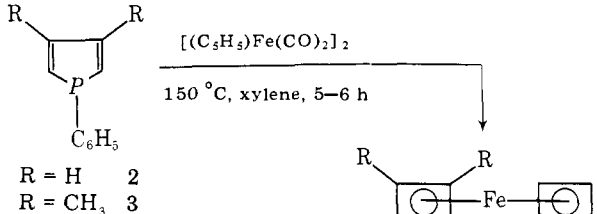
(1) S. Turner in "The Design of Organic Synthesis", Elsevier, New York, N.Y., 1976, p 217.
(2) M. Hamberg and B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.*, **70,** 899 (1973); M. Hamberg, J. Svensson, T. Wakabayashi, and B. Samuelsson, *ibid.*, **71,** 345 (1974); M. Hamberg, J. Svensson, and B. Samuelsson, *ibid.*, **72,** 2994 (1975).
(3) Other synthetic PGH_2 analogues reported to date are (a) 9,11-(–C≡C–)-type: P. Wlodawer, B. Samuelsson, S. M. Albonico, and E. J. Corey, *J. Am. Chem. Soc.*, **93,** 2815 (1971); E. J. Corey, M. Shibasaki, K. C. Nicolaou, C. L. Malmsten, and B. Samuelsson, *Tetrahedron Lett.*, 737 (1976); H. Shimomura, A. Sugie, J. Katsube, and H. Yamamoto, *ibid.*, 4099, (1976); (b) 9,11-(–N=N–)-type: E. J. Corey, K. C. Nicolaou, Y. Machida, C. L. Malmsten, and B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.*, **72,** 3355 (1975); (c) 9,11-(–OCH_2–)-type: G. L. Bundy, *Tetrahedron Lett.*, 1957 (1975); (d) 9,11-{–(EtOOC)C=C(COOEt)–}-type: A. G. Abatjoglou and P. S. Portoghese, *ibid.*, 1457 (1976).
(4) This diol was prepared as follows: methyl (5*Z*,11β,13*E*,15*S*)-9-oxo-11,15-bis(2-tetrahydropyranyloxy)prosta-5,13-dienoate [D. M. Floyd et al., *Tetrahedron Lett.*, 3269 (1972)] → 9β-hydroxy 11β,15α-bis(2-tetrahydropyranyloxy) $PGF_{2\alpha}$ methyl ester (sodium borohydride in methanol at −40 °C) → the 9β-acetoxy product (100% yield, acetic anhydride-pyridine at 25 °C for 12 h) → the 11β,15α-diol (83% yield, aqueous acetic acid) → the 9β,11β-diacetoxy-15α-ol (61% yield, first with diethyl(trimethylsilyl)amide in acetone followed by acetylation using acetyl chloride in pyridine and then acidic workup) → the 15α-(2-tetrahydropyranyl) ether (100%, dihydropyrane) → the 9β,11β-diol **2** (100%, potassium carbonate in methanol at 40 °C for 1 h).
(5) Other oxidation methods (i.e., via air oxidation or hydrogen peroxide) were unsuccessful.
(6) T. J. Wallace, *J. Org. Chem.*, **31,** 1217 (1966).
(7) NMR ($CDCl_3$) δ 5.80–5.10 (m, 4 H), 4.22–3.90 (m, 1 H), 3.88–3.72 (m, 1 H), 3.67 (s, 3 H), 3.55–3.40 (m, 1 H), 2.86–2.57 (m, 2 H); IR (liquid film) 3450, 1735, 970 cm^{-1}.
(8) G. L. Ellman, *Arch. Biochim. Biophys.*, **82,** 70 (1959).
(9) Successive spraying with sodium borohydride in ethanol followed by Ellman reagent elicited a strong, positive result; see G. Zweig and J. Sherma, Ed., "Handbook of Chromatography", Vol. 2, The Chemical Rubber Co., Cleveland, Ohio, 1972, p 151.
(10) This compound was synthesized by the method previously reported; see M. Hayashi and T. Tanouchi, *J. Org. Chem.*, **38,** 2115 (1973).
(11) J. T. Chandler and C. G. Strong, *Arch. Int. Pharmacodyn.*, **197,** 123 (1972).
(12) N. G. Ardlie, M. A. Packham, and J. F. Mustard, *Brit. J. Haematol.*, **19,** 7 (1970).
(13) Endodisulfides 1 and **7** did not inhibit the formation of PGH_2, whereas, 9α,11α-dimercapto $PGF_{2\alpha}$ methyl ester, readily available by deprotection of compound **5,** specifically inhibited PGH_2 biosynthesis. These results will be published elsewhere.
(14) Analogue 1 was stable in cyclhexane–ethyl acetate in the presence of Kiesel gel for at least 5 days.
(15) Biological degradation of cyclic disulfide 1 in vivo is under investigation.

Hajimu Miyake, Sadahiko Iguchi
Hiroyuki Itoh, Masaki Hayashi*
Ono Pharmaceutical Co., Ltd., Research Institute
Shimamoto, Osaka, Japan
Received December 16, 1976

Phosphaferrocene

Sir:

Recently Braye and Joshi[1] have described an attempted synthesis of a tetraphenyl-substituted phosphaferrocene by reaction of potassium 2,3,4,5-tetraphenylphospholyl with cyclopentadienyldicarbonyliron iodide. The $CpFe(CO)_2L$ σ complex thus formed (L = phospholyl) was stable and did not lose CO upon heating to give the expected phosphaferrocene. This stands in sharp contrast to observations when L = pyrrolyl (see the synthesis of azaferrocene[2]). In view of our recent success in the synthesis of phosphacymantrenes,[3] we thought that the failure of Braye and Joshi was not due to an intrinsic instability of the phosphaferrocene system but, more probably, to the high electron-withdrawing ability of the tetraphenyl substitution which destabilized the desired π-aromatic complex. Since the synthesis of phospholyl anions[4] does not give very satisfactory results with the less substituted *P*-phenylphospholes, we studied the reaction of these phospholes with dicyclopentadienyltetracarbonyldiiron, **1.** We expected a cleavage of the P-phenyl bond of *P*-phenylphospholes in the same way as with decacarbonyldimanganese.[3] Indeed, reactions of an equimolecular amount of **1** in boiling xylene at 150 °C with the phospholes **2** and **3**[5] afford, inter alia, the expected phosphaferrocenes **4** and **5,** respectively.



R = H 2
R = CH_3 3

4 yield ~30% mp ~152 °C dec
5 ~20% 78 °C

Both phosphaferrocenes are orange solids which appear to be less stable than the corresponding phosphacymantrenes. They are recovered from the reaction mixture by column chromatography (silica gel 60 merck, 70–230 mesh). They form an orange band which is eluted first by a benzene–hexane mixture (20–80).[6]

We give hereafter their ^1H NMR and mass spectral data. Other data (analytical, IR, and ^{13}C and ^{31}P NMR) will be reported elsewhere. ^1H NMR (60 MHZ, $CDCl_3$, internal Me_4Si): **4** δ 4.03 (d of m, J_{H-P} = 38 Hz, Hα), 4.35 (s, C_5H_5),

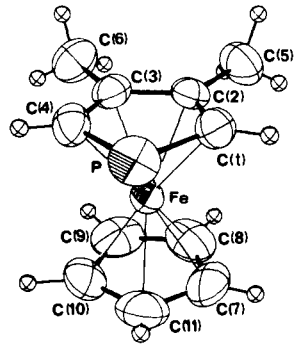
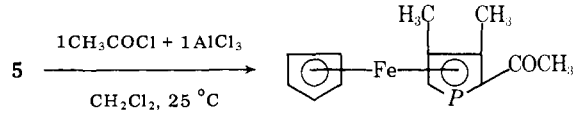


Figure 1. Structure of the phosphaferrocene **5** showing the 50% probability ellipsoids. Selected bond distances (in Å) are: C(1)-C(2), 1.408 (7); C(2)-C(3), 1.414 (6); C(3)-C(4), 1.403 (7); P-C(1), 1.758 (5); P-C(4), 1.768 (5); C(2)-C(5), 1.503 (8); C(3)-C(6), 1.516 (8); C(7)-C(8), 1.378 (12); C(8)-C(9), 1.411 (9); C(9)-C(10), 1.412 (10); C(10)-C(11), 1.393 (10); C(11)-C(7), 1.399 (10); Fe-P, 2.276 (1); -C(1), 2.064 (4); -C(2), 2.046 (4); -C(3), 2.040 (4); -C(4), 2.051 (4); -C(7), 2.046 (6); -C(8), 2.036 (7); -C(9), 2.027 (6); -C(10), 2.039 (5); -C(11), 2.045 (4).

5.25 (overlapping d of m, $J_{H-P} \sim 6$ Hz, Hβ); **5** δ 2.17 (s, CH_3), 3.71 (d, $J_{H-P} = 36$ Hz, Hα), 4.13 (s, C_5H_5). Mass spectra (70 eV, 40 °C; main peaks only): **4** *m/e* 204 (*I* = 100%, M), 139 (*I* = 13%, M-C_5H_5), 121 (*I* = 14%, M-C_4H_4P), 56 (*I* = 14%, Fe); **5** *m/e* 232 (*I* = 100%, M), 166 (*I* = 17%, M-C_5H_6), 121 (*I* = 8%, M-C_6H_8P), 56 (*I* = 10%, Fe).

Preliminary experiments have shown that **5** can be selectively acetylated on the phospholyl moiety:



6

The site of acylation was unambiguously established on the basis of the ^{1}H NMR spectrum of **6:** δ 2.18 (s, $CH_3\beta'$), 2.28 (d, $J_{H-P} \sim 2.6$ Hz, $COCH_3$), 2.43 (s, $CH_3\beta$), 4.03 (d, $J_{H-P} =$ 36 Hz, 1 H, CHP), 4.13 (s, 5 H, C_5H_5).

The chemical data thus clearly suggest a π-aromatic nature for the phospholyl ligand. This nature was unequivocally proved by the x-ray study of **5.**

Suitable crystals of **5** were obtained by vacuum sublimation at 40 °C. They belong to the monoclinic system, space group $P2_1/c-C_{2h}^5$) with $a = 12.292$ (4) Å, $b = 10.824$ (3) Å, $c =$ 7.831 (2) Å, $\beta = 91.60$ (4) °, $Z = 4$, and $\rho_c = 1{,}48$ g/cm^3.

Diffraction data were collected in a $\theta/2\theta$ scan mode using a Picker diffractometer and monochromated Mo Kα radiation. The structure was solved by direct methods[7] and refined to convergence using 1279 reflections having $I \geq 3\sigma(I)$. The value for the conventional agreement factor $R_F = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ at the present stage of refinement is 0.041.

The structure (Figure 1) consists of discrete molecules in which an iron atom is sandwiched between a π bonded cyclopentadienyl ring and a π bonded phospholyl group so as to attain an eclipsed conformation.

The phospholyl ligand is not strictly planar; the phosphorus atom lies out of the strictly planar four-membered carbon moiety by 0.041 (2) Å away from the iron atom. Selected geometric details are given in the caption of Figure 1.

The planar cyclopentadienyl ring and the planar four-membered carbon moiety C_4(P) of the phospholyl are nearly parallel, the dihedral angle is 3.18°. The iron atom is located somewhat closer to the C_4(P) plane: Fe···C_4(P) = 1.625 (1) Å whereas Fe···C_5H_5 = 1.655 (1) Å.

Acknowledgment. One of us (F.M.) thanks Mrs. Maillet for technical assistance.

References and Notes

(1) E. H. Braye and K. K. Joshi, *Bull. Soc. Chim. Belg.*, **80**, 651 (1971).
(2) K. K. Joshi, P. L. Pauson, A. R. Qazi, and W. H. Stubbs, *J. Organomet. Chem.*, 1, 471 (1964).
(3) F. Mathey, *Tetrahedron Lett.*, 4155 (1976).
(4) E. H. Braye, I. Caplier, and R. Saussez, *Tetrahedron*, **27**, 5523 (1971).
(5) F. Mathey and R. Mankowski-Favelier, *Bull. Soc. Chim. Fr.*, 4433 (1971); *Org. Magn. Reson.*, **4**, 171 (1972).
(6) The chromatographed products still contain minute amounts of ferrocene. They can be purified further by recrystallization in methanol at low temperature.
(7) Program MULTAN, P. Main, MM Woolfson, and G. Germain.
(8) Laboratoire de chimie structurale associé au C.N.R.S.

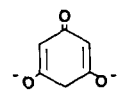
François Mathey*
Institut National de Recherche Chimique Appliquée
91710 Vert-Le-Petit, France

André Mitschler, Raymond Weiss*
Institut Le Bel[8]*-Université Louis Pasteur*
67070 Strasbourg-Cedex, France
Received December 22, 1976

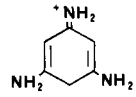
The Dependence of Phenol–Dienone Tautomerism upon the Hydrogen Bonding Characteristics of the Solvent: 3,5-Dipyrrolidinophenol

Sir:

The observation that the dianion of phloroglucinol exists predominately as the cyclohexa-2,5-dienone (**1**),[1] and the monoprotonated form of 1,3,5-triaminobenzene as the analogous form **2**[2] suggests the intriguing possibility that appro-

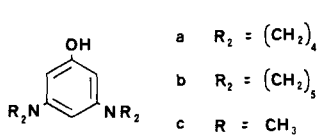


1

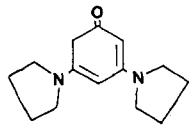


2

priately substituted benzenes may exist preferentially as such a structure in a nonionic state. In the course of his extensive investigations of polyamino benzenes, Effenberger examined a series of 3,5-diaminophenols, **3a–c**, with this point in mind.[3]



3



4

However, ^{1}H NMR spectra of these materials in dimethyl sulfoxide solution showed only aromatic forms present. Strikingly, the ultraviolet absorption reported for 3,5-dipyrrolidinophenol, **3a**, showed a maximum at 370 nm, with an extinction coefficient of 3050 L mol^{-1} cm^{-1} in methanol.[3] We show here that this absorption is characteristic of a cyclohexa-2,4-dienone form, **4**, which may predominate in solvents of appropriate hydrogen-bonding character.

The ultraviolet absorption spectra of **3a** in three solvents are shown in Figure 1. The absorption in dimethyl sulfoxide is that of a phenol, corresponding to the form shown by the ^{1}H NMR spectrum, but that in water shows a maximum at 375 nm ($\epsilon =$ 15 300). As it seemed reasonable to speculate that it is the ability of water to donate a hydrogen bond which stabilizes the carbonyl group of the dienone form, a solvent was sought which retains this ability, while being capable of dissolving enough of **3a** to allow study by NMR spectra. Trifluoroethanol proved to be suitable.[4]

The addition of trifluoroethanol to a deuteriochloroform solution of **3a** caused increasing amounts of olefinic absorption