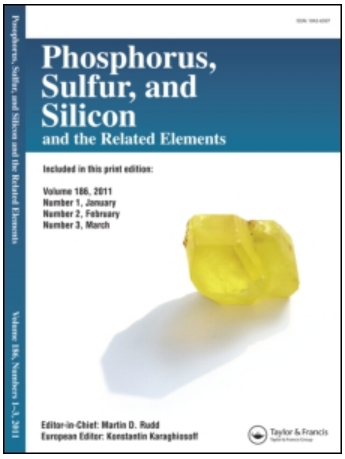


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# A FACILE NOVEL ACCESS TO THE ISOPHOSPHINDOLINE SYSTEM

Ekkehard Fluck[ab]; Ralf Riedel[ab]; Peter Fischer[c]
[a] Institut für Anorganische Chemie der Universität Stuttgart, Stuttgart 80 [b] Gmelin-Institut für Anorganische Chemie der Max-Planck-Gesellschaft, Frankfurt 90 [c] Institut für Organische Chemie, Biochemie und Isotopenforschung der Universität Stuttgart, Stuttgart 80

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# A FACILE NOVEL ACCESS TO THE ISOPHOSPHINDOLINE SYSTEM

EKKEHARD FLUCK† and RALF RIEDEL

*Institut für Anorganische Chemie der Universität Stuttgart, Pfaffenwaldring 55, D–7000 Stuttgart 80, und Gmelin-Institut für Anorganische Chemie der Max-Planck-Gesellschaft, Varrentrappstraße 40/42, D-6000 Frankfurt 90*

PETER FISCHER

*Institut für Organische Chemie, Biochemie und Isotopenforschung der Universität Stuttgart, Pfaffenwaldring 55, D-7000 Stuttgart 80*

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Synthesis of a novel isophosphindoline derivative, 1-phenyl-1,3-dihydro-2$\lambda^5$-benzophospholic acid (**1**), is described, the structure of **1** established on the basis of $^{13}C$, $^{1}H$, and $^{31}P$ NMR spectra, and the NMR and mass spectral data are discussed in detail.

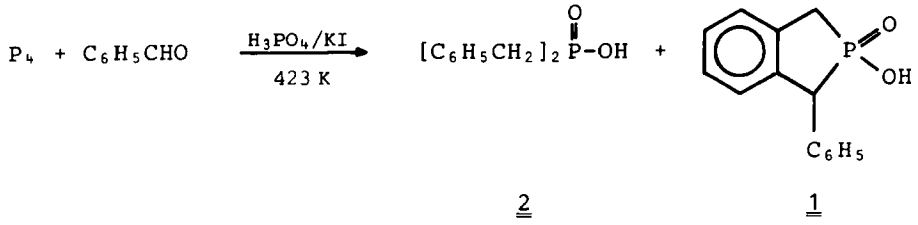


## INTRODUCTION

Isophosphindoline itself was first synthesized in 1973, starting from *o*-xylenedibromide, *via* a five-step-sequence in very moderate overall yield.[1] Other approaches to the isophosphindoline skeleton which have far better yields employ the McCormack reaction as one of several steps.[2,3] Further preparative procedures have been reviewed by Quin.[4]

## SYNTHESIS OF 1 AND MECHANISM OF FORMATION

We have now found a facile, one-pot-reaction access to this interesting heterocyclic system when we investigated the reduction of aromatic aldehydes with white phosphorus. If benzaldehyde is reacted with $P_4$ in concentrated phosphoric acid and in the presence of potassium iodide, 1-phenyl-1,3-dihydro-2$\lambda^5$-benzophospholic acid (**1**) is formed, under the proper reaction conditions, in 23% yield, besides dibenzylphosphinic acid (**2**) and, eventually, small quantities of benzylphosphonic acid.




**2** **1**

† Author to whom all correspondence should be addressed.

The—*prima facie* surprising—formation of **1** is readily understood if one considers the individual steps and intermediates in this reaction sequence. At elevated temperatures in the system $P_4/H_3PO_4/KI$, white phosphorus is converted into phosphorous and, principally, hypophosphorous acid which, with 2 moles of benzaldehyde, forms bis($\alpha$-hydroxybenzyl)phosphinic acid[5] in a kind of hetero aldol condensation. This intermediate in turn is reduced by iodide to dibenzylphosphinic acid (**2**) as reported by Ettel and Horak.[6]

We observe the identical sequence for our highly acidic system in which, however, the $\alpha$-hydroxy group of bis($\alpha$-hydroxybenzyl)phosphinic acid can be protonated concurrently. Subsequent cleavage of $H_2O$ leaves a well-stabilized benzylic carbenium ion which, by intramolecular Friedel-Crafts alkylation of the other benzyl ring, finally affects ring closure to the benzophospholic acid **1**. The **2**:**1** ratio under our experimental conditions is 1:2.5 (determined by $^1$H NMR integration).

Aromatic aldehydes with Cl or $CH_3$ substituents in positions 2 and 6, which are thus blocked for electrophilic attack, indeed do not form cyclic derivatives but only open-chain phosphinic acids.



## NMR AND MASS SPECTRAL PROOF OF STRUCTURE 1

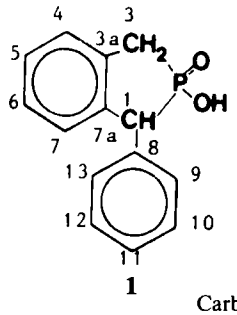
The structure of the reaction product **1** has been established unequivocally on the basis of its $^{31}$P, $^1$H, and principally $^{13}$C NMR spectra. The $^{13}$C NMR data of **1**, together with those of dibenzylphosphinic acid **2** and of P-methyl isophosphindolinoxide **3**,[3] are listed in Table I, those of the diastereoisomeric methyl esters **4a**, **b** in Table II (for preparation of **4a**, **b**, see Reference 7). The definitive assignment of the individual aryl carbon resonances of **1** was accomplished by comparing the 22.63 and 75.47 MHz $^{13}$C spectra, and in part with reference to the respective resonances of **4a**, **b**.

The fully coupled $^{31}$P spectrum shows a broad pseudo-quartet at 59.6 ppm ($\nu_{1/2}$ 8.5 Hz, $J_{app}$ 14.5 Hz) which, upon selective decoupling of all aryl protons, is resolved into a doublet of triplets ($\nu_{1/2}$ 3.0 Hz, $^2J$(PCH) 16.5; 13.0 Hz). These identical coupling constants appear in the $^1$H spectrum.

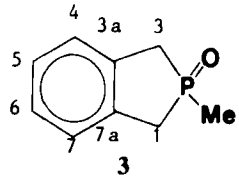
In the noise-decoupled $^{13}$C spectrum of **1**, there are two saturated carbon signals which are split by $^1J$(CP) couplings of 88 and 85 Hz, respectively,[8] and which, on the evidence of the DEPT spectrum, indeed pertain to one $CH_2$ and CH carbon each as required by the $^{31}$P multiplicity. Relative to dibenzylphosphinic acid, the $CH_2$ resonance is shifted upfield by 9 ppm, indicating an especially large $\gamma$ effect due to another C-H moiety in fixed cisoid orientation (see Figure 1). The aryl carbon signals are all but two split into doublets by long-range C,P coupling. Three of them originate from quaternary carbons, as demonstrated by off-resonance and DEPT spectra, but only two have double intensity: the product molecule thus may contain only one mono-substituted, freely rotating phenyl moiety. For the four different carbon positions of this phenyl ring, C,P coupling constants remain virtually unchanged from those in the open-chained structure **2** (see Table I). The carbon atoms in the annulated benzo ring of **1**, on the other hand, display remarkably large C,P long range couplings which by

TABLE I

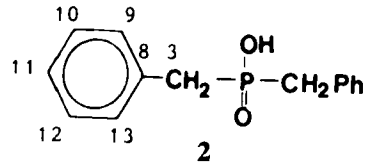
$^{13}C$ NMR data[a] of compounds **1**, **2**, and **3**,[3] $\delta$ [ppm] ($J_{CP}$ [Hz])



**1**



**3**



**2**

| Carbon atom | **1** | **3** | **2** |
|---|---|---|---|
| 1 | 49.95 (85.0) | 34.5 (65.9) | |
| 3 | 31.53 (88.0) | 34.5 (65.9) | 40.44 |
| 3a | 135.43 (11.0) | 135.0 (10.4) | |
| 4 | 127.12 (15.0) | 127.4 (11.6) | |
| 5 | 127.20 (—) | 127.8 (—) | |
| 6 | 127.20 (—) | 127.8 (—) | |
| 7 | 126.74 (13.5) | 127.4 (11.6) | |
| 7a | 140.34 (14.5) | 135.0 (10.4) | |
| 8 | 136.89 (6.0) | | 137.05 (8.5) |
| 9, 13 | 129.22 (5.0) | | 133.77 (5.5) |
| 10, 12 | 128.15 (2.0) | | 132.02 (2.0) |
| 11 | 126.34 (1.5) | | 130.00 (—) |

[a] Data from spectra, run on a Bruker CXP 300 Ip, at 75.47 MHz nominal frequency, with a sweep width of 17857.143 Hz and 32 k interferograms and transforms, digital resolution 1.1 Hz/point ≙ 0.01 ppm/point.



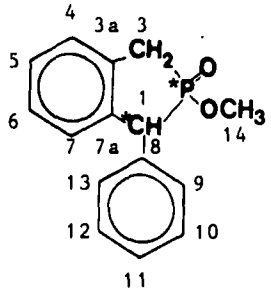
themselves constitute proof of the bicyclic structure. So, $^3J$(CP) for C-4 and C-7 (15 and 13.5 Hz, respectively) traverses an s-trans pathway which represents the optimum orientation for the Fermi contact mechanism. Both quaternary carbons, C-3a and C-7a (11 and 14.5 Hz), are linked to the $^{31}P$ nucleus via a twofold, $^2J/^3J$ coupling path.

The EI mass spectra of **1** and of the mixture of the diastereoisomeric methyl esters **4a**, **b** present virtually identical patterns (see Table III). An intensive $M^{+\cdot}$ signal indicates that direct loss of $H_2O$ or $CH_3OH$ is not an important fragmentation process. The dominant ion cluster at $m/z$ 180 to 178 corresponds to the anthracene-derived structures **5**–**7**, with comparable relative intensities for all three ions (the intensity missing for $m/z$ 178 has been transferred to the doubly charged ion $C_{14}H_{10}^{+\cdot+}$). This fragmentation pattern, which also includes fluorenyl mono- and dication ($m/z$ 165 and 82.6, respectively) and dibenzocyclobutadiene radical cation and dication ($m/z$ 152 and 76) is well known from stilbene where it has been studied in all mechanistic details.[9] This close identity in fragmentation definitely proves that the two aryl subunits in **1** and **4a**, **b** have been linked directly, as in stilbene, prior to isomerization of the MS generated ion.

This is demonstrated even more strikingly in a CI($CH_4$)–GC/MS spectrum

TABLE II

$^{13}C$ NMR data[a] of the two diastereoisomeric methyl esters **4a, b**, $\delta$ [ppm] ($J_{CP}$[Hz])




| Carbon atom | **4a**[b] | **4b**[b] |
|---|---|---|
| 1 | 49.10 (87.9) | 50.60 (83.7) |
| 3 | 30.19 (89.1) | 31.02 (89.8) |
| 3a | 134.38 (12.3) | 134.41 (12.3) |
| 4 | 127.84 (15.0) | 127.38 (14.3) |
| 5 | 128.10 (2.1) | 127.90 (2.3) |
| 6 | 128.08 (1.7) | 127.82 (1.2) |
| 7 | 127.35 (17.2) | 127.11 (18.2) |
| 7a | 139.40 (15.7) | 139.02 (15.4) |
| 8 | 136.26 (5.3) | 135.10 (9.4) |
| 9, 13 | 129.06 (5.3) | 129.46 (4.8) |
| 10, 12 | 128.79 (2.5) | 128.72 (2.6) |
| 11 | 127.18 (3.0) | 127.32 (3.2) |
| 14 | 51.89 (6.7) | 51.80 (6.7) |

[a] see footnote[a], Table I

[b] Assignment of the individual resonances to **4a** and **4b**, respectively, is based on the $^{13}C$ spectrum of a 2:1 mixture which had been partially resolved by liquid chromatography (see Reference 7).



where the two diastereoisomeric methyl esters **4a, b** were run in one batch, i.e. under absolutely identical ionization conditions, with methyl dibenzylphosphinate. Loss of $CH_3OH$ is negligible for all three compounds as in the EI spectra. Apart from quasi-molecular and adduct ions, the benzyl or tropylium ion, $m/z$ 91, is the only intensive signal in the dibenzylphosphinate spectrum. In the CI mass spectrum of **4a, b** on the other hand, the $C_7H_7$ ion carries at the most 1% relative intensity. The complete absence of benzyl cleavage ultimately proves the

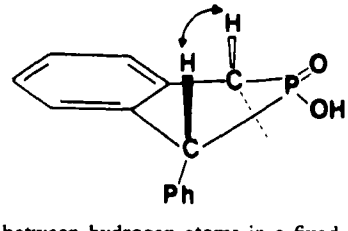



FIGURE 1 *γ-cis* Interaction between hydrogen atoms in a fixed cisoid orientation at C-1 and C-3 of **1**.

TABLE III

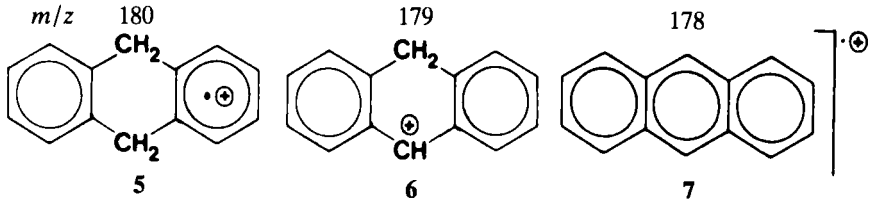
Mass spectral data[a] of the isophosphindoline derivatives **1** and **4a, b**

| **1** $m/z$ ($I_{rel}$) | Fragment ion | **4a, b** $m/z$ ($I_{rel}$) |
|---|---|---|
| 245 (11.4) | $M^{+\cdot}(^{13}C)$ | 259 (12.7) |
| 244* (71.8) | $M^{+\cdot}$ | 258* (76.2) |
| | $(M - CH_3)^+$ | 243 (4.0) |
| 226* (3.0) | $C_{14}H_{11}PO^{+\cdot}$ | 226 (2.8) |
| | $(M - H_2O/CH_3OH)$ | |
| 181 (15.0) | $C_{14}H_{12}^{+\cdot}(^{13}C)$ | 181 (16.6) |
| 180* (99.4) | $C_{14}H_{12}^{+\cdot}$ | 180 (100.0) |
| 179* (100.0) | $C_{14}H_{11}^+$ | 179 (99.6) |
| 178* (53.7) | $C_{14}H_{10}^{+\cdot}$ | 178 (51.9) |
| 177 (7.2) | $C_{14}H_9^+$ | 177 (6.4) |
| 176* (8.4) | $C_{14}H_8^{+\cdot}$ | 176 (7.4) |
| 166 (5.1) | $C_{13}H_9^+(^{13}C)$ | 166 (4.6) |
| 165*(32.6) | $C_{13}H_9^+$ | 165 (31.9) |
| 152* (8.8) | $C_{12}H_8^{+\cdot}$ | 152 (6.4) |
| 89.6 (8.0) | $C_{14}H_{11}^{++}/C_{14}H_{10}^{+\cdot\cdot}(^{13}C)$ | 89.6 (5.6) |
| 89*(30.2) | $C_{14}H_{10}^{+\cdot\cdot}$ | 89 (23.2) |
| 82.6 (6.0) | $C_{13}H_9^{++}$ | 82.6 (3.6) |
| 76.5 (2.0) | $C_{12}H_8^{+\cdot\cdot}(^{13}C)$ | |
| 76 (15.6) | $C_{12}H_8^{+\cdot\cdot}$ | 76 (12.6) |

[a] 70 eV, source temperature 420 K

* ion composition established by high resolution mass determination

intramolecular junction of the two original $C_6H_5CH_2$ moieties in **4a, b**, and thence of course in **1**.




5 6 7

## EXPERIMENTAL

NMR spectra were measured on a Bruker CXP 300, in PFT technique, with 75.47 MHz ($^{13}C$) and 121.49 MHz ($^{31}P$) nominal frequency. Chemical shifts are reported as $\delta$ values, relative to 85% aqueous orthophosphoric acid for $^{31}P$, and relative to tetramethylsilane as internal standard for $^1H$ and $^{13}C$.

Mass spectra in EI mode were recorded on a Varian MAT 711 mass spectrometer; exact masses were determined by the peak matching technique with perfluorokerosene (PKF) ions as internal reference. CI mode GC/MS spectra were run on a Finnigan 4023 spectrometer, coupled directly to a Carlo Erba 2150 gas chromatograph, and equipped with an Incos 2300 data system.

*Preparation of* 1-*phenyl*-1,3-*dihydro*-2$\lambda^5$-*benzophospholic acid* (**1**). In a three-necked round-bottom flask, equipped with a reflux condenser and magnetic stirrer, 200 ml conc. phosphoric acid, 6.7 g (40 mmoles) KI, and 100 g (943 mmoles) benzaldehyde are heated to 150°C. 20 g (645 mmoles) white phosphorus are added in 0.5 g portions. It is essential that each piece of phosphorus has completely reacted before the next piece is added. In the course of the addition, the temperature is slowly raised to 190°C. The reaction mixture is then allowed to cool, and extracted three times with 200 ml $CH_2Cl_2$ each. The combined organic phases are washed with water, dried over $Na_2SO_4$, filtered, and

concentrated in a rotary evaporator. The residue is recrystallized from 300 ml ethanol, and finally washed with 400 ml ethanol/water (1:1).

Yield: 27 g **1** (23% on the basis of benzaldehyde), m.p. 203–205°C.

$C_{14}H_{13}O_2P$ (244.2): calc. C 68.85, H 5.36, P 12.68; found C 68.51, H 5.49, P 12.46.

$^{31}P$ NMR (DMSO-$d_6$): 59.6 ppm.

$^{1}H$ NMR ($CDCl_3$): 3.0 ppp (d, $^{2}J$(PCH) 14 Hz, $CH_2$), 4.4 ppm (d, $^{2}J$(PCH) 17 Hz, CH), 6.9 ppm (m, aromatic protons).

$^{13}C$ NMR: see Table I.

IR (nujol and hostaflon mull, respectively, $cm^{-1}$): 3056 w, 3026 w, 2975 w, 2935 vw, 2910 m, 2020 s(b), 1600 vs(b), 1495 m, 1478 m, 1452 m, 1402 w, 1300 w, 1210 vs, 1139 vs, 1080 vs, 1036 m, 998 vs, 978 vs, 918 m, 885 w, 875 m, 830 s, 819 s, 788 m, 768 m, 752 s, 724 m, 712 s, 699 s, 603 m, 563 m, 514 s, 491 s, 475 vs, 430 s, 412 s, 340 m.

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