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# 3-(4-Phosphoryl-4-methyl-2-oxopentyl)-3-hydroxyindolin-2-ones, the first phosphorus analogues of natural convolutamydines

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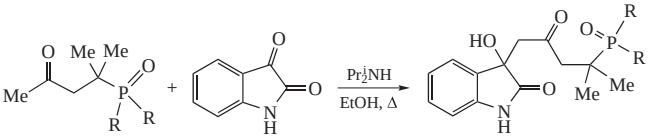
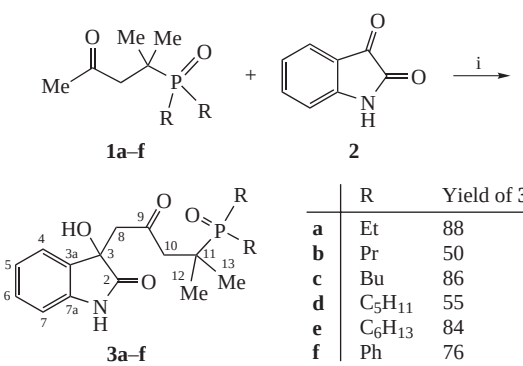
**The first examples of phosphorus-containing analogues of natural alkaloids, convolutamydines, have been obtained by aldol condensation of 4-[dialkyl(diphenyl)phosphoryl]-4-methylpentan-2-one with isatin. An unusually facile reversible process of dehydration–hydration of these phosphorus-containing hydroxy indoles has been discovered.**




Isatin derivatives show a broad spectrum of biological activity, *e.g.*, antimicrobial, antitumor, anti-HIV ones.[1–3] Furthermore, the high reactivity of carbonyl group at 3-position and benzo moiety are important factors determining the broad application of isatins in organic synthesis.[4–10] We have found previously that conjugation of isoniazid, an anti-tuberculosis agent, with dimephosphon [dimethyl (2-methyl-4-oxopent-2-yl)phosphonate], a known antiacidotic and metabolic agent,[11] or with its P–C analogues, dialkyl(2-methyl-4-oxopent-2-yl)phosphine oxides,[12] considerably reduces the toxicity of the conjugates without decreasing the pharmaceutical effect of isoniazid.[13,14] Here we report a synthesis of the first representatives of organophosphorus analogues of natural alkaloids, convolutamydines. It is known that the use of a catalytic amounts of a base in the reaction of isatin with aliphatic and fatty-aromatic ketones does not cause opening of the isatin ring driving the process towards cross-aldol condensation between the activated carbonyl group of isatin (the carbonyl component) and a methyl (methylene) group of a ketone (the methylene component). The products of these reactions are convolutamydine analogues possessing a broad range of biological activity.[15–18]

In this study, we have found that 4-[dialkyl(diphenyl)phosphoryl]-4-methylpentan-2-ones **1a–f** can undergo aldol condensation with isatin **2** to give phosphorus-containing analogues of convolutamydines **3a–f** (Scheme 1).† The reaction proceeds in refluxing ethanol in the presence of catalytic amounts (2–3 drops) of diisopropylamine.




| | R | Yield of **3** (%) |
|---|---|---|
| **a** | Et | 88 |
| **b** | Pr | 50 |
| **c** | Bu | 86 |
| **d** | $C_5H_{11}$ | 55 |
| **e** | $C_6H_{13}$ | 84 |
| **f** | Ph | 76 |

**Scheme 1** *Reagents and conditions:* i, Pr$^i_2$NH, EtOH, 78 °C, 12–24 h.

It should be noted that despite the presence of two reactive sites (methyl and methylene groups) in phosphoryl ketones **1**, the reaction occurs exclusively at the methyl group, apparently due to steric factors. In the $^1$H NMR spectra of 3-hydroxyindolin-2-ones **3**, the signals of the $H^8$ and $H^{10}$ methylene protons are most characteristic. The $H^8$ protons are diastereotopic due to the effect of a chiral centre in the molecule and resonate as two related doublets 3.01 ppm (d, $H^{8A}$, $J_{AB}$ 15.9 Hz) and 3.17 ppm (d, $H^{8B}$, $J_{BA}$ 15.9 Hz). The $H^{10}$ methylene protons appear as a strongly broadened doublet 2.57 ppm (d, $^3J_{PH}$ 8.1 Hz). The chemical shifts and multiplicity of the other aliphatic protons are, in general, similar to those for analogous phosphine oxides reported previously.[12] The IR spectra of compounds **3** are characterized by absorption bands corresponding to the C=O groups of the ketone (1710–1715 cm$^{-1}$) and amide (~1720 cm$^{-1}$) moieties. The structure of diethylphosphoryl representative **3a** was confirmed by X-ray diffraction (Figure 1).‡

† *3-[4-Dialkyl(diphenyl)phosphoryl-4-methyl-2-oxopentyl]-3-hydroxyindolin-2-ones* (*typical procedure*). A mixture of isatin (0.147 g, 1.0 mmol), phosphoryl ketone **1a–f** (1.0 mmol, for their synthesis see ref. 12) and a few drops of Pr$^i_2$NH in EtOH (5 ml) was stirred at 78 °C for 12–24 h. The reaction progress was monitored by TLC (EtOAc as an eluent, phosphine oxide **1** as a standard). After appropriate time (see Online Supplementary Materials), a solvent was rotary evaporated. The residue was purified by dry column flash chromatography (KSKG silica gel < 0.063 mm, eluent EtOAc for starting compounds and impurities, and ethanol for products).

‡ *Crystal data for* **3a**·2 $CHCl_3$ . $C_{20}H_{28}C_{l6}NO_4P$, $M$ = 590.10, monoclinic, space group $P2_1/n$, $a$ = 14.963(12), $b$ = 10.812(8) and $c$ = 17.689(14) Å, $\beta$ = 96.715(15)°, $V$ = 2842(4) Å$^3$, $Z$ = 4, $d_{calc}$ = 1.379 g cm$^{-3}$. Total of 13456 reflections were measured on a Bruker Smart Apex II CCD diffractometer using graphite monochromated MoKα radiation at 293(2) K. Absorption corrections based on the Laue symmetry using equivalent reflections were applied, $\mu$ = 0.686 mm$^{-1}$. The structure was solved by direct methods using SHELXT[19] and refined by full-matrix least-squares on $F^2$ using SHELXL[20] with 5084 unique reflections, $R_{int}$ = 0.1531. Non-hydrogen atoms were refined anisotropically. The hydrogen atoms were inserted at the calculated positions and refined as riding atoms. The disorder of a chloroform molecule

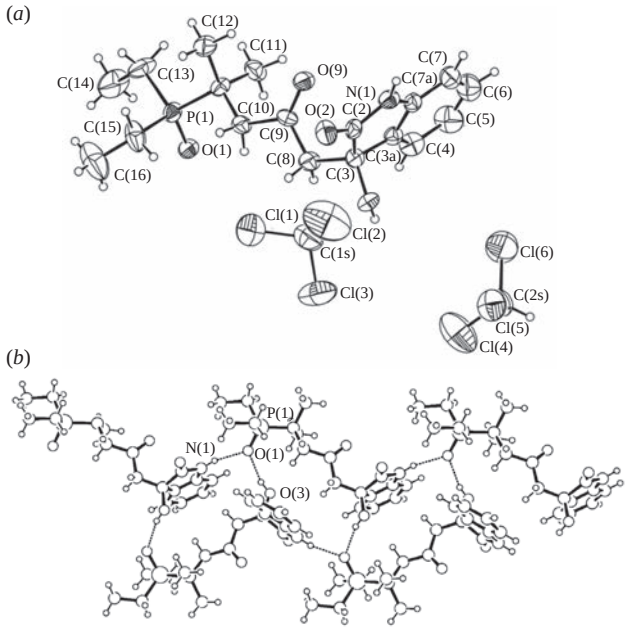
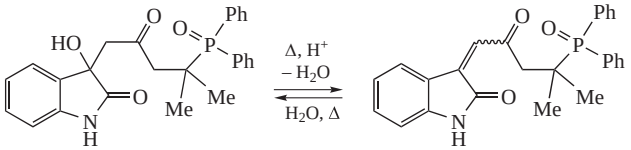



**Figure 1** (*a*) ORTEP diagram showing 30% probability anisotropic displacement ellipsoids of non-hydrogen atoms for compound **3a**·2 $CHCl_3$ according to single crystal X-ray diffraction data. (*b*) A fragment of molecular packing in the crystals of **3a**·2 $CHCl_3$ viewed along axis 0*c*. The chloroform molecules are omitted for clarity.

Compound **3a** crystallizes with two chloroform molecules in monoclinic space group $P2_1/n$ as a racemic compound. One of the chloroform molecules is almost equally disordered into two components. The molecular structure of **3a** is characterized by a tetrahedral coordination of the P(1) phosphorus atom and the presence of one chiral center C(3). The geometry of the symmetrically independent molecule **3a** is shown in Figure 1(*a*). The main supramolecular motif in the crystals of **3a**·2 $CHCl_3$ is a one-dimensional homochiral ribbon oriented along the shortest axis 0*b*. The ribbon is constructed from two chains joined by the intermolecular hydrogen bonds P(1)–O(1)···H(3)–O(3), while the chains are formed by the P(1)–O(1)···H(1)–N(1) intermolecular hydrogen bonds. A fragment of molecular packing of **3a** in the crystals is presented in Figure 1(*b*). Due to the dispersion interactions of peripheral fragments mainly with chloroform molecules that act as a connecting mediator, the one-dimensional ribbons are connected into a three-dimensional heterochiral crystal structure.

After purification of diphenylphosphoryl representative **3f** by chromatography (ethyl acetate, then ethanol as the eluents) and during the rotary evaporation of the solvent, the colour changed from light yellow to red. As a result, α,β-enone **4**, a product of dehydration of aldol **3f**, was the only isolated compound (Scheme 2).

Probably, the presence of trace amounts of acetic acid in ethyl acetate was sufficient to affect the dehydration of hydroxyindolin-2-one **3f**. Similar cases are known, but regularly they require more harsh conditions (heating in acetic acid in the presence




**Scheme 2**

of catalytic amounts of mineral acids).[16] $^1$H NMR spectrum of compound **4** contains no multiplet of diastereotopic protons $H^{8A,8B}$; the methylene protons $H^{10}$ resonate as a doublet at 3.06 ppm with $^3J_{PH}$ 8.0 Hz, while the lower-field region contains a singlet of the alkene $H^8$ proton 7.06 ppm (s, 1H, $H^8$). Compound **4** was formed as a single isomer, however, configuration of its double bond was not a topic of this study. We have found that dissolution of compound **4** in a $CDCl_3$–DMSO-$d_6$ mixture with slight heating results in hydration of compound **4** to recover aldol **3f**. Apparently, on heating, water present in DMSO adds at the double bond of compound **4**.§

In conclusion, we have accomplished syntheses of 3-[4-dialkyl(diaryl)phosphoryl-4-methyl-2-oxopentyl]-3-hydroxyindolin-2-ones, the first phosphorus-containing analogues of natural alkaloids, convolutamydines. The compounds obtained seem promising as low-toxic materials with a broad spectrum of biological activity.

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*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.05.021.

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was resolved with the help of free variables and reasonable restraints on geometry and anisotropic displacement parameters. Refinement of 327 parameters converged to $R_1 = 0.1334$, $wR_2 = 0.2838$ for 1642 reflections with $I > 2\sigma(I)$ and $R_1 = 0.2830$, $wR_2 = 0.3524$ for all data with $S = 1.180$ and residual electron density, $\rho_{max/min} = 0.585$ and –0.654 eÅ$^{-3}$. Diffraction from the crystal was poor, especially at high theta angles. Moreover, analysis of collected data suggested that the crystal was transformed during data collection, probably owing to loss of chloroform or phase transition. Hence, only images of the first two $\omega$-scans were processed. In spite of high residual factors, the expected molecular structure was confirmed.

CCDC 1583268 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

§ *3-(4-Diphenylphosphoryl-4-methyl-2-oxopentylidene)indolin-2-one* **4**. A light yellow solution of compound **3f** in EtOH with an admixture of EtOAc and AcOH was rotary evaporated (bath temperature 60 °C, 200 mbar) to give a deep red residue of compound **4** in quantitative yield.

*3-(4-Diphenylphosphoryl-4-methyl-2-oxopentyl)-3-hydroxyindolin-2-one* **3f**. Enone **4** was dissolved in a mixture of $CDCl_3$ and DMSO-$d_6$ (70 : 30) with an admixture of $H_2O$ under heating (60 °C). During the dissolution, hydration occurred, accompanied by a color change from deep red to light yellow to give compound **3f** in quantitative yield.

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