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## Phosphorus, Sulfur, and Silicon and the Related Elements

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## The Preparation and Anticancer Activity of Some Phosphorus Heterocycles

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## The Preparation and Anticancer Activity of Some Phosphorus Heterocycles

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*Methods for the preparation of some phosphorus heterocycles are reviewed, together with a preliminary report of their activity in vitro against the NCI 60-cell line panel of human tumour cells. The most active compound, a dimer of 3-methyl-1-(2,4,6-triisopropylphenyl)phosphole oxide, showed GI<sub>50</sub> values in the micromolar region against leukaemia cell lines RPMI-8226 and SR, non-small cell lung cancer (NCI-H460), colon cancer (COLO 205), and melanoma (SK-Mel-5 and UACC-62).*

**Keywords** Anticancer; dihydrophosphinine; NCI; organophosphorus; phosphanorbornene; phosphole oxide; phosphorus heterocycle; tetrahydrophosphinine

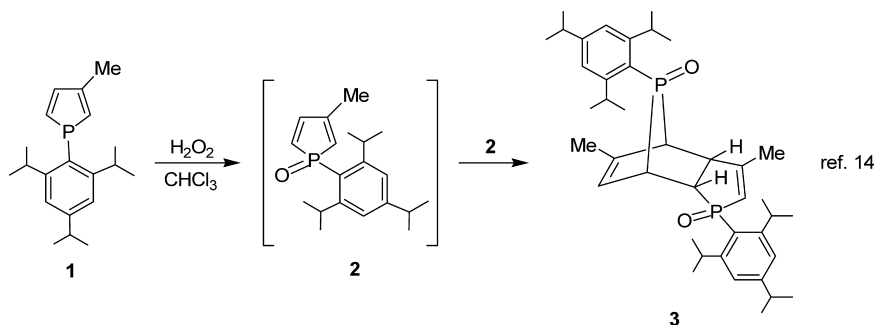
## INTRODUCTION

Chemotherapy is an important aspect of the treatment of cancer.<sup>1</sup> The numbers and types of compound that have been reported to show anticancer activity are legion and numerous new examples are constantly under investigation.<sup>2</sup> Those that have become established in clinical use<sup>3</sup> include organophosphorus compounds such as cyclophosphamide<sup>4</sup> (a nitrogen mustard) and related phosphoramidate derivatives such as ifosfamide and thiotepa, all of which act as alkylating agents and cause DNA cross-linking.<sup>5</sup> Other types of organophosphorus compound that exhibit anticancer activity include various phosphonic and phosphinic acid derivatives,<sup>6</sup> e.g., nucleoside phosphonates,<sup>5</sup> aminophosphonates,<sup>7</sup> bisphosphonic acid derivatives,<sup>8</sup>

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SCHEME 1

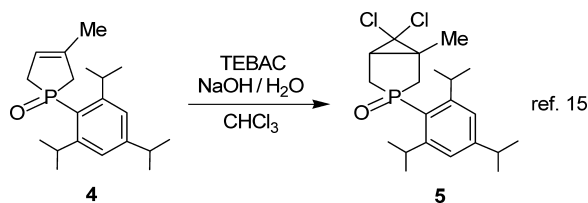
phosphonocarboxylate-platinum complexes,<sup>9</sup> and aminophosphonate-platinum complexes.<sup>10</sup>

We report here an overview of the preparation and activity of the phosphole oxide derivatives **3** and **5**, and of a number of dihydrophosphinines (**8a-c** and **13a,c-e**) and tetrahydrophosphinines (**14f-h** and **15**), which have been subjected to in vitro screening at the National Cancer Institute (NCI).<sup>11</sup> Anticancer activity has not previously been reported for compounds of these types.

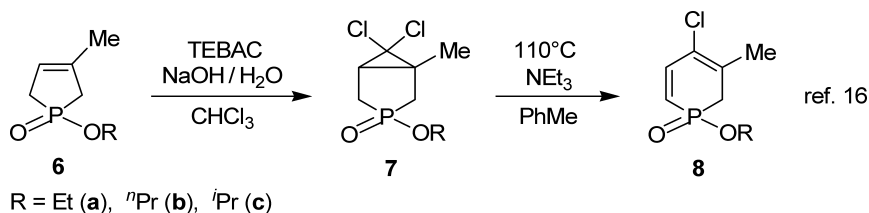
## SYNTHETIC METHODS

In the last two decades, a number of families of phosphorus heterocycles have been described.<sup>12,13</sup>

Within the group of 7-phosphanorbornene derivatives, the phosphole oxide dimer **3** with sterically demanding 2,4,6-triisopropylphenyl substituents at the phosphorus atoms was prepared. The phosphole **1** was converted to the corresponding phosphole oxide **2**, which underwent a regio- and stereospecific dimerization to afford product **3** (Scheme 1).<sup>14</sup> 2,5-Dihydro-1*H*-phosphole oxides **4** and **6a-c** were subjected to dichlorocarbene addition to give 3-phosphabicyclo[3.1.0]hexane 3-oxides **5** and **7a-c**, respectively, in both cases as a mixture of two diastereomers (Schemes 2 and 3).<sup>15,16</sup> The opening of the cyclopropane ring



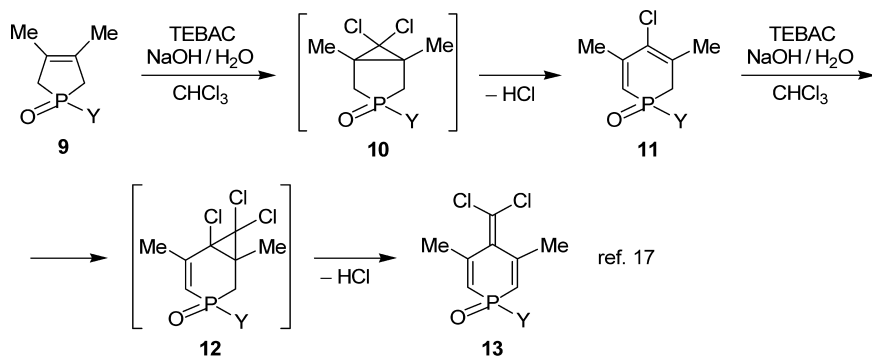
SCHEME 2

**SCHEME 3**

of dichlorocarbene adducts **7a-c** led to the predominant formation of 1,2-dihydrophosphinine 1-oxides **8a-c** (Scheme 3).<sup>16</sup>

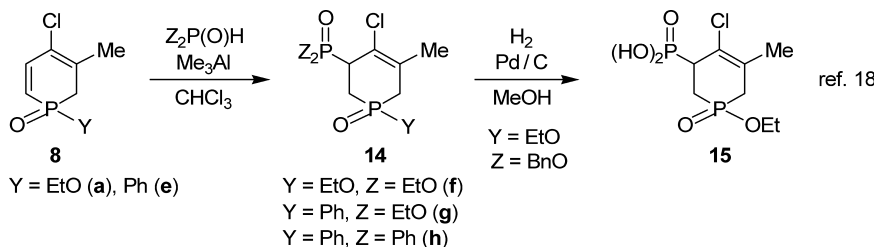
The dichlorocarbene addition reaction of 3,4-dimethyl-2,5-dihydro-1*H*-phosphole oxides **9a,c-e** furnished surprisingly the 4-dichloromethylene-1,4-dihydrophosphinine oxides **13a,c-e** (Scheme 4). In this instance, the 3-phosphabicyclo[3.1.0]hexane oxide **10a,c-e** underwent a spontaneous cyclopropane ring opening to provide 1,2-dihydrophosphinine oxide **11**. The latter underwent a dichloro-cyclopropanation to give **12**, which afforded **13** by cyclopropane ring opening and the loss of hydrogen chloride.<sup>17</sup>

Diethyl phosphite and diphenylphosphine oxide were added to the electron-poor double-bond of 1,2-dihydrophosphinine oxides **8a** and **8e** after activation with trimethylaluminum. Products of the phosphamichael reaction were the 3-phosphonato- and 3-diphenylphosphin-oxido-1,2,3,6-tetrahydrophosphinine oxides **14f,g** and **14h**, respectively (Scheme 5).<sup>18</sup> The addition was diastereoselective. Hydrogenolysis of the dibenzyl ester (**14**, Y=Et, Z=BnO) gave the phosphonic acid **15**.<sup>18</sup>



Y = EtO (a), <sup>i</sup>PrO (c), <sup>n</sup>BuO (d), Ph (e)

**SCHEME 4**



SCHEME 5

## ANTICANCER ACTIVITY

Compounds **3**, **5**, **8a-c** and **13a,c-e** were tested in vitro against the NCI 60-cell line panel of human tumour cells at a maximum concentration level of  $10^{-4}$  molar, and at four lower concentrations, each at successive 10-fold dilutions down to  $10^{-8}$  molar. The results, which are summarized in Table I, show average response parameters over all cell lines of  $GI_{50}$  between  $2.1 \times 10^{-6}$  and  $7.32 \times 10^{-5}$  M, TGI between  $6.63 \times 10^{-6}$  and  $9.84 \times 10^{-5}$  M, and  $LC_{50}$  between  $2.7 \times 10^{-6}$  and  $1.0 \times 10^{-4}$  M. The most active compound overall was the phosphanorbornene derivative **3** for which  $GI_{50}$  values in the region of  $1-1.5 \times 10^{-6}$  molar were recorded in duplicate experiments against leukaemia cell lines RPMI-8226 and

**TABLE I** Anticancer Activity in 60 Cell Line 5-Dose Screening for Compounds **3**, **5**, **8**, **13**, **14**<sup>a</sup>

	Average over all cell lines (M) <sup>b</sup>		
	$GI_{50}$	TGI	$LC_{50}$
<b>3</b>	$2.10 \times 10^{-6}$	$6.63 \times 10^{-6}$	$2.70 \times 10^{-6}$
<b>5</b>	$8.66 \times 10^{-6}$	$2.16 \times 10^{-5}$	$5.27 \times 10^{-5}$
<b>8a</b>	$1.48 \times 10^{-5}$	$3.81 \times 10^{-5}$	$7.46 \times 10^{-5}$
<b>8b</b>	$3.30 \times 10^{-5}$	$7.48 \times 10^{-5}$	$9.48 \times 10^{-5}$
<b>8c</b>	$7.32 \times 10^{-5}$	$9.84 \times 10^{-5}$	$1.00 \times 10^{-4}$
<b>13a</b>	$1.06 \times 10^{-5}$	$4.58 \times 10^{-5}$	$8.81 \times 10^{-5}$
<b>13c</b>	$4.71 \times 10^{-5}$	$8.67 \times 10^{-5}$	$9.60 \times 10^{-5}$
<b>13d</b>	$7.50 \times 10^{-6}$	$2.92 \times 10^{-5}$	$7.64 \times 10^{-5}$
<b>13e</b>	$6.13 \times 10^{-6}$	$2.37 \times 10^{-5}$	$7.08 \times 10^{-5}$

<sup>a</sup>Data from the DTP website (<http://dtp.nci.nih.gov>), where full information is given for compounds **3** (NSC 709166), **5** (NSC 709160), **8a** (NSC 639390), **8b** (NSC 644257), **8c** (NSC 639391), **13a** (NSC 644259), **13c** (NSC 648099), **13d** (NSC 648100), and **13e** (NSC 624332).

<sup>b</sup>Molar concentrations for 50% growth inhibition ( $GI_{50}$ ), total growth inhibition (TGI), and 50% kill ( $LC_{50}$ ).

**TABLE II Percentage Growth (Relative to Control) in One Dose 60 Cell Line Assay for Compounds 14 and 15, at Single Dose Level of  $10^{-5}$  M<sup>a</sup>**

	Leukemia CCRF-CEM	Leukemia HL-60 (TB)	Renal cancer UO-31
<b>14f</b>	−27.48	—	—
<b>14g</b>	−90.63	—	—
<b>14h</b>	47.59	28.77	—
<b>15</b>	−35.59	11.46	42.48

<sup>a</sup>Negative values indicate the level of kill. Positive values indicate growth inhibition by at least 50%.

SR, non-small cell lung cancer (NCI-H460), colon cancer (COLO 205), and melanoma (SK-Mel-5 and UACC-62). The mode of action is not known. Attempts to gain an insight into possible mechanisms of action by means of the NCI program COMPARE<sup>19</sup> revealed no satisfactory correlations with standard agents.

One dose 60 cell line assay was carried out at a concentration of  $10^{-5}$  molar for the tetrahydrophosphinines **14f–h** and **15**, which were found to be less active. In most cases the percent growth was not changed significantly under these test conditions but some exceptions, for which limited activity was detected, are shown in Table II.

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