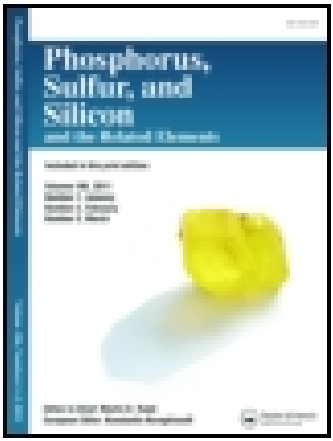


Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

The Preparation and Anticancer Activity of Some Phosphorus Heterocycles

Harry R. Hudson [a] & György Keglevich [b]

[a] Department of Health and Human Sciences , London Metropolitan University , London, UK

[b] Department of Organic Chemistry and Technology , Budapest University of Technology and Economics , Budapest, Hungary

Published online: 12 Aug 2008.

To cite this article: Harry R. Hudson & György Keglevich (2008) The Preparation and Anticancer Activity of Some Phosphorus Heterocycles, Phosphorus, Sulfur, and Silicon and the Related Elements, 183:9, 2256-2261, DOI: 10.1080/10426500801938592

To link to this article: http://dx.doi.org/10.1080/10426500801938592

Phosphorus, Sulfur, and Silicon, 183:2256–2261, 2008

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500801938592

Taylor & Francis
Taylor & Francis Group

The Preparation and Anticancer Activity of Some Phosphorus Heterocycles

Harry R. Hudson[1] and György Keglevich[2]
[1]Department of Health and Human Sciences, London Metropolitan University, London, UK
[2]Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Budapest, Hungary

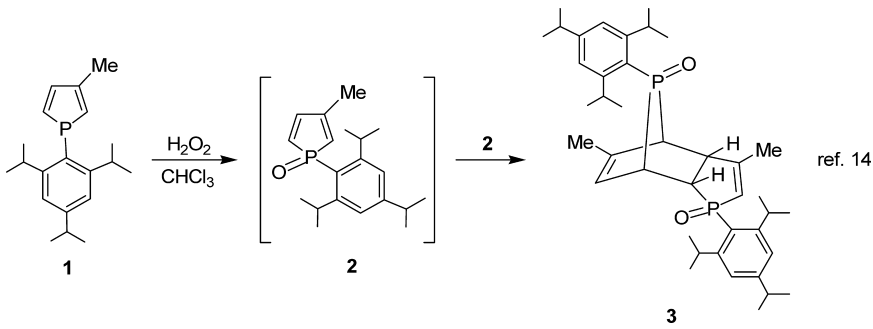
Methods for the preparation of some phosphorus heterocycles are reviewed, together with a preliminary report of their activity in vitro against the NCI 60-cell line panel of human tumour cells. The most active compound, a dimer of 3-methyl-1-(2,4,6-triisopropylphenyl)phosphole oxide, showed GI_{50} values 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.[1] The numbers and types of compound that have been reported to show anticancer activity are legion and numerous new examples are constantly under investigation.[2] Those that have become established in clinical use[3] include organophosphorus compounds such as cyclophosphamide[4] (a nitrogen mustard) and related phosphoramide derivatives such as ifosfamide and thiotepa, all of which act as alkylating agents and cause DNA cross-linking.[5] Other types of organophosphorus compound that exhibit anticancer activity include various phosphonic and phosphinic acid derivatives,[6] e.g., nucleoside phosphonates,[5] aminophosphonates,[7] bisphosphonic acid derivatives,[8]

Received 17, January 2008; accepted 20, January 2008.
We thank the National Cancer Institute[11] for anticancer screening and for the biological data reported in this paper. This project was also supported by the Hungarian Scientific Research Fund (OTKA Grant No. T067679).
Address correspondence to György Keglevich, Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Budapest 1521, Hungary. E-mail: keglevich@mail.bme.hu



SCHEME 1

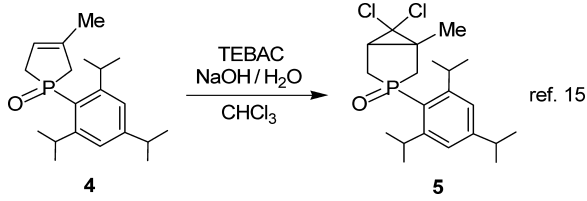
phosphonocarboxylate-platinum complexes,[9] and aminophosphonate-platinum complexes.[10]

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).[11] Anticancer activity has not previously been reported for compounds of these types.

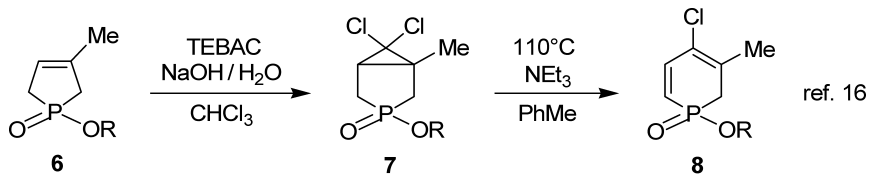
SYNTHETIC METHODS

In the last two decades, a number of families of phosphorus heterocycles have been described.[12,13]

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).[14] 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).[15,16] The opening of the cyclopropane ring



SCHEME 2



6 **7** **8**

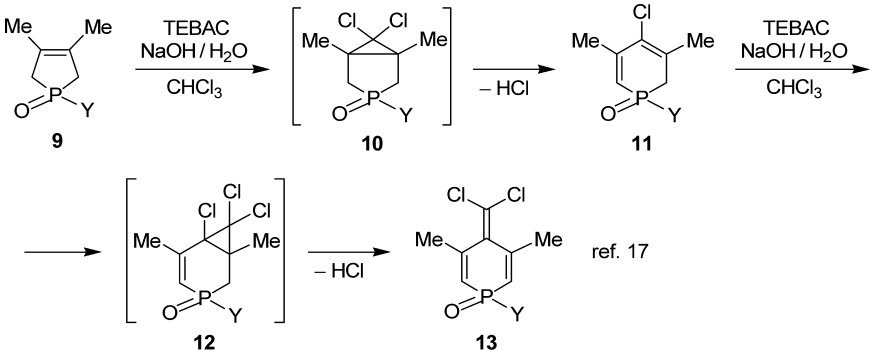
R = Et (**a**), ^{n}Pr (**b**), ^{i}Pr (**c**)

SCHEME 3

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

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 dichlorocyclopropanation to give **12**, which afforded **13** by cyclopropane ring opening and the loss of hydrogen chloride.[17]

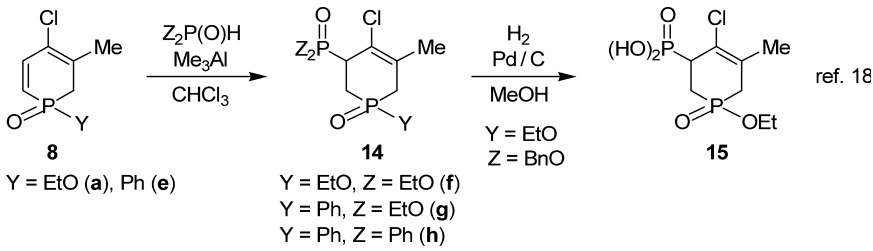
Diethyl phosphite and diphenylphosphine oxide were added to the electron-poor double-bond of 1,2-dihydrophosphinine oxides **8a** and **8e** after activation with trimethylaluminum. Products of the phospha-Michael reaction were the 3-phosphonato- and 3-diphenylphosphinoxido-1,2,3,6-tetrahydrophosphinine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



9 **10** **11** **12** **13**

Y = EtO (**a**), ^{i}PrO (**c**), ^{n}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 2.1×10^{-6} and 7.32×10^{-5} M, TGI between 6.63×10^{-6} and 9.84×10^{-5} M, and LC_{50} between 2.7×10^{-6} and 1.0×10^{-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[a]

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

[a]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).

[b]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[a]

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

[a]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[19] 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.

REFERENCES

[1] R. T. Skeel, *Handbook of Cancer Chemotherapy* (Lippincott Williams and Wilkins, Philadelphia, 2007), 7th ed.

[2] (a) H. Wang, J. Klinginsmith, X. Dong, A. C. Lee, R. Guha, Y. Wu, G. M. Crippen, and D. J. Wild, *J. Chem. Inf. Model.*, **47,** 2063 (2007); (b) D. G. Covell, R. L. Huang, and A. Wallqvist, *Mol. Cancer Ther.*, **6,** 2261 (2007).

[3] *Martindale, The Complete Drug Reference*, S. C. Sweetman, Ed. (Pharmaceutical Press, London 2006), 35th ed.

[4] O. M. Colvin, *Curr. Pharm. Des.*, **5,** 555 (1999).

[5] N. J. Wardle, S. W. A. Bligh, and H. R. Hudson, *Curr. Org. Chem.*, **9,** 1803 (2005).

[6] (a) D. Dus, E. Wojdat, C. Radzikowski, and P. Mastalerz, *Archivum Immunologiae et Therapie Experimentalis*, **33,** 325 (1985); (b) A. Kalir, and H. H. Kalir, In *The Chemistry of Organophosphorus Compounds*, F. R. Hartley, Ed. (Wiley, Chichester, 1996), Vol. 4, Ch. 9, pp. 774–775.

[7] (a) B. Wysocka-Skrzela, *Pol. J. Chem.*, **56,** 1573 (1982); (b) B. Lejczak, D. Dus, and P. Kafarski, *Anti-Cancer Drug Design*, **5,** 351 (1990); (c) J. L. Fischel, M. Berlion, P. Formento, J. P. Bizzari, and G. Milano, *European Journal Of Cancer*, **9A,** 1890 (1993); (d) R. -Y. Chen and L. J. Mao, *Phosphorus, Sulfur, and Silicon*, **89,** 97 (1994); (e) P. Kafarski and B. Lejczak, *Curr. Med. Chem. –Anti-Cancer Agents*, **1,** 301 (2001); (f) B. Song, S. Yang, Y. P. Hong, G. P. Zhang, L. H. Jin, and D. Y. Hu, *J. Fluorine Chem.*, **126,** 1419 (2005); (g) L. H. Jin, B. Song, G. P. Zhang, R. Q. Xu, S. M. Zhang, X. W. Gao, D. Y. Hu, and S. Yang, *Bioorg. Med. Chem. Lett.*, **16,** 1537 (2006); (h)

E. Naydenova, K. Troev, M. Topashka-Ancheva, G. Hägele, I. Ivanov, and A. Kril, *Amino Acids*, **33,** 695 (2007); (i) B. Wang, Z. W. Miao, J. Wang, R. Y. Chen, and X. D. Zhang, *Amino Acids*, (Springer, Wien, 2007), online First, July 31.

[8] (a) S. Boissier, M. Ferreras, O. Peyruchaud, S. Magnetto, F. H. Ebetino, M. Colombel, P. Delmas, J. M. Delaisse, and P. Clezardin, *Cancer Res.*, **60,** 2949 (2000); (b) A. M. Forsea, C. Muller, C. Riebeling, C. E. Orfanos, and C. C. Geilen, *British J. Cancer*, **91,** 803 (2004); (c) P. Clezardin, F. H. Ebetino, and P. G. J. Fournier, *Cancer Res.*, **65,** 4971 (2005); (d) A. J. Roelofs, P. A. Hulley, A. Meijer, F. H. Ebetino, R. Graham, G. Russell, and C. M. Shipman, *Internat. J. Cancer*, **119,** 1254 (2006); (e) J. Sonnemann, B. Bumbul, and J. F. Beck, *Mol. Cancer Ther.*, **6,** 2976 (2007); (f) V. Stresing, F. Daubine, I. Benzaid, H. Wonkkonen, and P. Clezardin, *Cancer Lett.*, **257,** 16 (2007).

[9] L. S. Hollis, A. V. Miller, A. R. Amundsen, J. E. Schurig, and E. W. Stern, *J. Med. Chem.*, **33,** 105 (1990).

[10] M. J. Bloemink, J. J. H. Diederen, J. P. Dorenbos, R. J. Heetebrij, B. K. Keppler, and J. Reedjik, *Eur. J. Inorg. Chem.*, 1655 (1999).

[11] Compounds were selected for screening under the Developmental Therapeutics Program of the National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA (http://dtp.nci.nih.gov).

[12] Gy. Keglevich, *Synthesis*, 931 (1993), and references cited therein.

[13] Gy. Keglevich, *Curr. Org. Chem.*, **10,** 93 (2006), and references cited therein.

[14] Gy. Keglevich, L. D. Quin, Zs. Böcskei, Gy. M. Keserű, R. Kalgutkar, and P. M. Lahti, *J. Organomet. Chem.*, **532,** 109 (1997).

[15] Gy. Keglevich, Gy. M. Keserű, H. Forintos, Á. Szöllősy, K. Ludányi, and L. Tőke, *J. Chem. Soc. Perkin Trans. 1*, 1801 (1999).

[16] Gy. Keglevich, J. Brlik, F. Janke, and L. Tőke, *Heteroatom Chem.*, **1,** 419 (1990).

[17] Gy. Keglevich, L. Tőke, A. Kovács, G. Tóth, and K. Újszászy, *Heteroatom Chem.*, **4,** 61 (1993).

[18] Gy. Keglevich, M. Sipos, D. Szieberth, L. Nyulászi, T. Imre, K. Ludányi, and L. Tőke, *Tetrahedron*, **60,** 6619 (2004).

[19] K. D. Paull, R. H. Shoemaker, L. Hodes, A. Monks, D. A. Scudiero, L. Rubinstein, J. Plowman, and M. R. Boyd, *J. Natl. Cancer Inst.*, **81,** 1088 (1989).