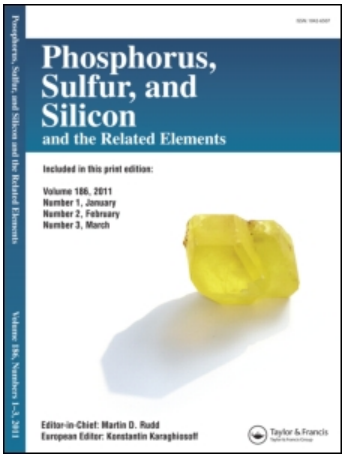

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ISOQUINO[2,1-*c*][1,3,2] BENZODIAZAPHOSPHORINE DERIVATIVES: NEW POTENTIAL AGENTS FOR CANCER CHEMOTHERAPY

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ISOQUINO[2,1-*c*][1,3,2] BENZODIAZAPHOSPHORINE DERIVATIVES: NEW POTENTIAL AGENTS FOR CANCER CHEMOTHERAPY

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Three derivatives of 2-chloro-5,8,9,13b-tetrahydro-5-methyl-6H-Isoquino[2,1-c][1,3,2]benzodiazaphosphorine 6-oxides as well as its sulphides were synthesized with the aim of evaluating their antitumor properties. Three of the twenty one compounds were found to be significantly active (inhibition of tumor growth > 80%) in the Ehrlich ascites carcinoma screen. Several structure-activity relationships were indicated for antitumor activity in this screen. An aziridinyl substituted derivative, bis-(2-chloroethyl)amino substitution (**3**) also exhibited significant activity against the growth of P-388 lymphocytic Leukemia cells in male BDF_1 mice (% T/C = 147; % T/C > 125 is considered significant). The reference for activity comparison is cyclophosphamide or cytoxan i.e. [bis(2-chloroethyl)amino]-5,6-dihydro-2H-1,3,2-oxazaphosphorinane 2-oxide [having T/C × 100 = 339 at a dose of 65 mg/kg]

Keywords: Diazaphosphorine; Synthesis; Antitumor-properties; Spectral elucidation; Structure-activity-relation

Dedicated to Prof. Dr. H. Gunther (University of Siegen) on the occasion of his 65th birthday in July 2000.

INTRODUCTION

Many naturally occurring and synthetic compounds that contain 1-benzylisoquinoline moiety have received attention in view of the clinical application of papaverine as an antipasmodic agent and several of these compounds have proven to be potent antineoplastic agents. A thorough lit-

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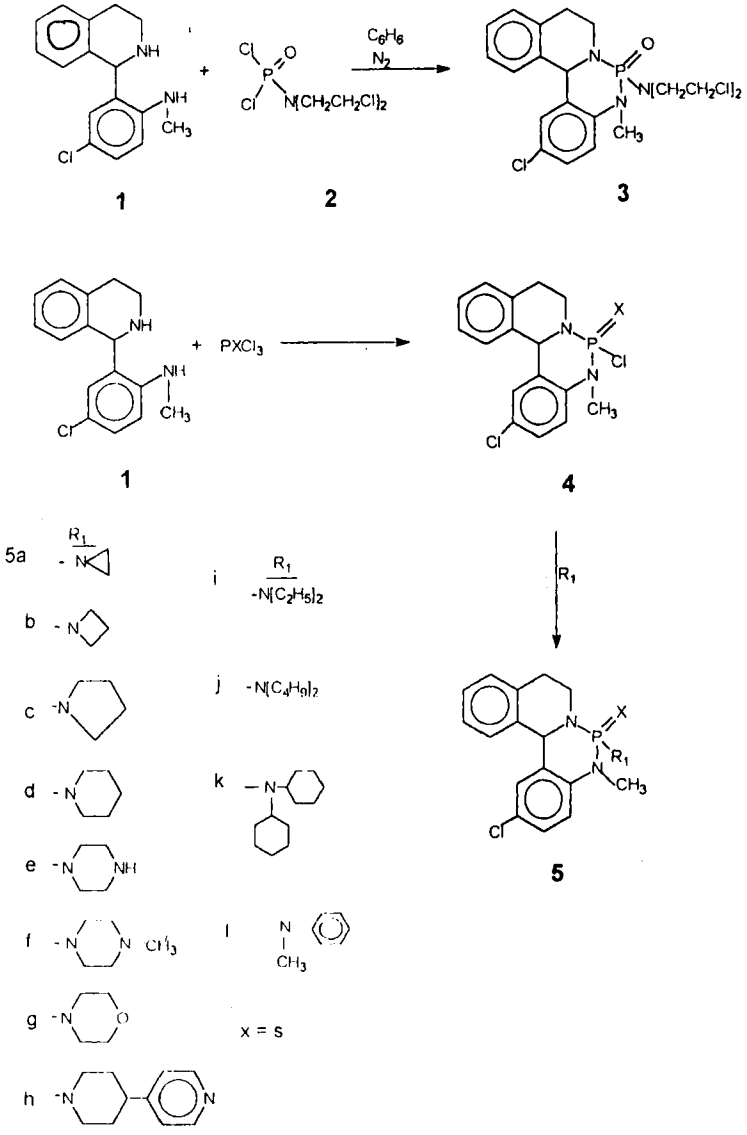
erature survey indicated that very little (precisely none) work has been done in evolving the organophosphonic derivatives of these 1-benzyl isoquinolines. Bradsher *et al.* (1985) reported the benzo[a,b]quinolizinium system[3] while Ott (1967) prepared the sulphur analogue 5,6,8,9-tetrahydro-13–1*H*-isoquinolo[2,1-c]quinazoline-6-thione.[4] These compounds have undergone clinical trials in Europe, Japan and the United States of America. Several derivatives of these interesting group of nitrogen containing heterocyclic isoquinolines have been reported as active against the growth of certain rodent tumors.[8,9] Our goal was to incorporate the bis-(2-chloroethyl)amino dichlorophosphate and several cyclic aminodichlorophosphate, aziridinyl dichlorophosphate and several cyclic aminodichlorophosphate into the 1-(o-aminophenyl)-1,2,3,4-tetrahydroisoquinoline system in an attempt to synthesize more potent antitumor agents. Previous studies in this laboratory[10–12] have shown that the heterocyclic derivatives of nitrogen, phosphorus and oxygen are anticancer agents and a good number of them (dioxaphospholes and dioxaphosphepins) find wide application as agricultural pesticides and insecticides.

RESULTS AND DISCUSSION

The isoquino[2,1-c][1,3,2]benzodiazaphosphorine 2-oxides as well as their sulphides were synthesized by the condensation of 1-(o-aminophenyl)-1,2,3,4-tetrahydroisoquinoline (**1**) with bis-(2-chloroethyl)amino phosphoramidic dichloride (**2**) in dry benzene using the evolution of hydrogen chloride gas as the means of ensuring the completion of the reaction. Various cyclic amino dichlorophosphate were also condensed (Scheme 1) with **1** via a cyclic intermediate **4** which in itself showed appreciable activity as antitumor agent. These series of compounds showed an over all poor yield and were very difficult to purify by the normal recrystallization procedure. Purity was achieved by running the crude sample through a chromatographic column of silica gel while eluting with a mixture of benzene-ethyl acetate (4:1) mixture. All compounds were coloured granular solids melting within the range of 123° and 149° (Table I). All the reactions were carried out in ice-cold condition (-5°C) and in an inert atmosphere. Caution must be taken to ensure that all experiments are performed in a fume cupboard and the reaction mixture carried out in sealed flask since alkylating agents, reactants and products are potential carcinogens. The derivatives containing 8-hydroxyquinolino moiety and

aryloxy groups (Scheme 2) showed very little activity against the growth of P-388 Lymphocytic Leukemia cells in male mice (% T/C = < 55). Rather these derivatives of 8-hydroxyquinoline exhibited *in vitro* and *in vivo* inhibitory properties against acetylcholinesterase (ChE).

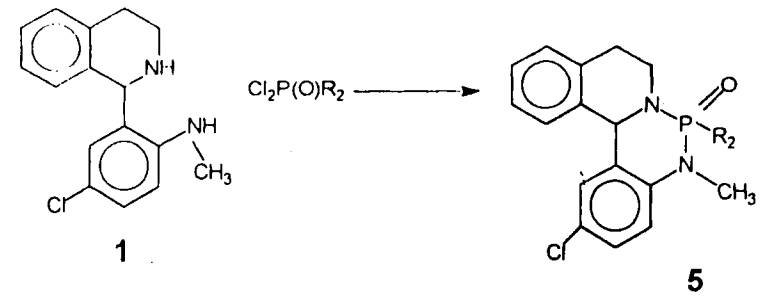


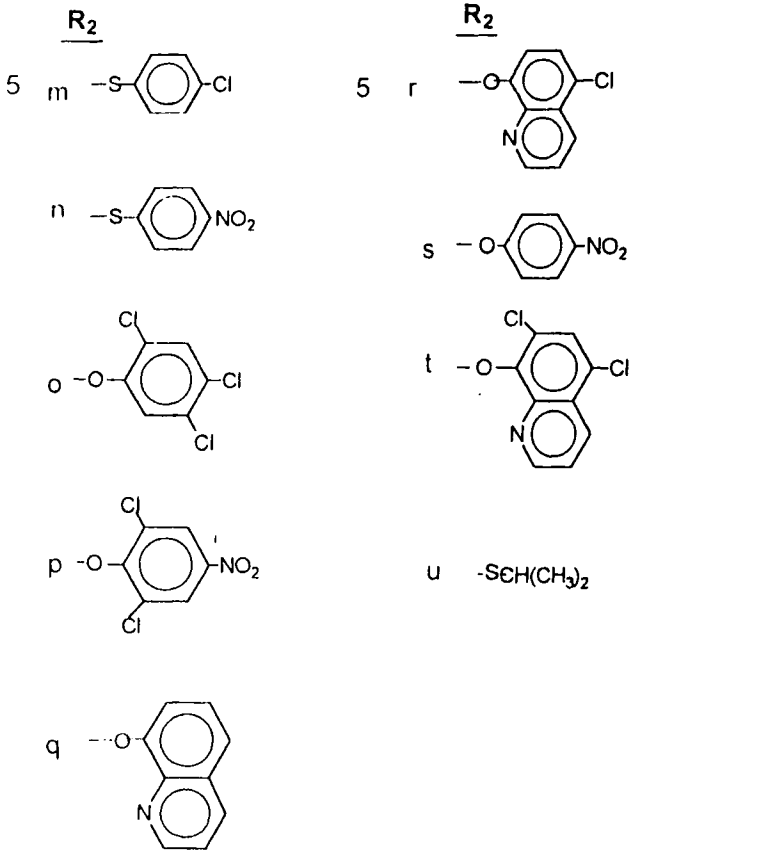
SCHEME 1

TABLE I Physical characteristic data of compounds **5a-5q**

Compounds	*M.P. °C*	*Yield %*	*Mol Formular*	*Found (%) (Calc)*		
				C	*H*	
5a	135–137	67	$C_{18}H_{19}N_3PSCl$	57.4	4.9	(57.5 5.0)
5b	131–133	73	$C_{19}H_{21}N_3PSCl$	57.9	5.1	(58.5 5.4)
5e	101–103	52	$C_{20}H_{29}N_4PSCl$	57.5	5.0	(57.3 5.7)
5f	146–147	66	$C_{21}H_{26}N_4PSCl$	59.0	5.9	(58.2 5.7)
5g	127–129	79	$C_{20}H_{23}N_3OPSCl$	56.8	5.9	(57.1 5.4)
5j	99–101	81	$C_{24}H_{33}N_3PSCl$	62.4	4.8	(62.4 4.8)
5q	76–78	70	$C_{25}H_{21}N_3O_2PCl$	62.9	4.6	(62.0 4.5)
5r	70–71	87	$C_{25}H_{20}N_3O_2PCl_2$	59.2	4.1	(60.4 4.0)
5t	81–83	94	$C_{25}H_{19}N_3O_2PCl_3$	57.9	4.1	(56.6 3.6)
3	105–107	69	$C_{20}H_{23}N_3OPSCl_3$	53.0	5.1	(52.4 5.0)
4	70–80	55	$C_{16}H_{15}N_2PSCl_2$	52.5	4.4	(52.0 4.4)
6	116–118	35	$C_{18}H_{20}N_3PSCl_2$	52.3	4.8	(52.4 4.8)

Facile substitution of the chlorine atom in the intermediate **4** with various cyclic amines such as ethylenimine, azetadine and pyrrolidine provided aziridinyl, azetadinyl and pyrrolidinyl compounds **5a, 5b** and **5c** respectively (scheme 1). Infrared and nuclear magnetic resonance spectra established the structures of the above series of compounds (Tables II and III). These compounds were unstable under electron impact mass spectra. In the IR spectra (recorded with KBr disc), these compounds exhibited characteristic absorption bands for P=O in the range 1320–1305 cm^{-1}; similar bands were observed in the region 789–712 (P=S), 1230–1225, 990–960 (P-O-$C_{aromatic}$), 1095–1670, 755–695 (P-N-$C_{aliphatic}$); and 1080–1040, 775–655 cm^{-1} (P-N-$C_{aromatic}$). Chemical shifts of some of the oxazaphosphorine synthesized are presented in Table II. The methyl protons resonated in the region δ1.5–2.7 as expected[13]. A multiplet due to the overlap of methine and methylene protons appeared as eight and five lines with the three outer lines appearing very weak in intensities. The appearance of this signals may be attributed to the coupling between phosphorus and the methine proton. Long range phosphorus and methylene coupling could be another factor giving rise to multiplets. The methylenes of the





SCHEME 2

cyclic amino groups were observed in the range of δ1.63–3.24 ppm. The methine protons are expected (but overlapped) within the region δ2.8–3.2. Aromatic protons are located between δ6.4–8.7. The electron impact process led to less stable molecular ion with low relative abundance. In some compounds, the molecular ion was not at all observed. The instability of the exocyclic P-N bond to the electron impact process in the spectra of benzodiazaphosphorine is contrary to that pointed out by Kulkarni[14], and this may have contributed to the greater low molecular ion. Cleavage of the aziridinyl ring in compound **5a** with HCl gas in absolute methanol afforded the 2-chloroethylamino derivative **6** (Scheme 3) in a 35% yield.

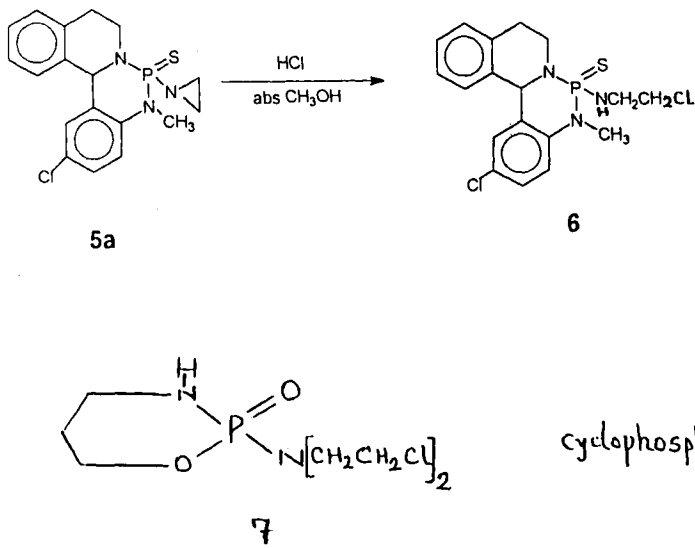
TABLE II ^{1}H NMR data of some of the titled compounds

Compound	*^{1}H NMR ($CDCl_3$)δ*			
	Methyl-H	*Methylene-H*	*Methine-H*	*Aromatic-H*
3	2.25 (s, CH_3)	2.6–3.6 (Br-m, 12H) ($6 \times CH_2$)	Overlaps with Methylene-H	6.5–7.2 (m, 7H)
4	1.5 (s, CH_3)	2.3–2.8 (m, 4H)	"	6.4–7.3 (m, 7H)
5a	1.9 (s, CH_3)	1.6 (s, 4H ie $2 \times CH_2$) 2.7–3.0 (d, 4H ie $2 \times CH_2$)	"	6.9–8.2 (m, 7H)
5e	2.0 (s, CH_3)	1.8 (s, 4H ie $2 \times CH_2$) 2.6–2.8 (d, 4H ie $2 \times CH_2$)	"	6.6–6.9 (m, 7H)
5h	2.2 (s, CH_3)	2.6–2.9 (m, 13H)	"	6.9–8.5 (m, 11H)
5l	2.4 (s, CH_3)	2.5–2.9 (d, 4H ie $2 \times CH_2$)	"	6.8–8.1 (m, 12H)
5I (d,	1.9–2.1 6H ie $2 \times CH_3$)	2.4–2.7 (Br-m, 16H, $8 \times CH_2$)	"	6.7–8.1 (m, 7H)
5q	2.3 (s, CH_3)	2.8–3.3 (m, 4H)	"	6.2–7.4; 8.3–8.7 (m, 13H)
5r	2.7 (s, CH_3)	2.9–3.1 (d, 4H ie $2 \times CH_2$)	"	6.4–7.6; 8.4–8.8 (m, 12H)
6	2.18 (s, CH_3)	2.4–2.7 (Br-m, 8H) (ie $4 \times CH_2$)	"	6.6–7.3 (m, 7H)

TABLE III Important fragments of some benzodiazaphosphorine 6-oxides and sulphides

Compound	M^+	*m/z (relative intensity)*
3	[a]	272(7.77), 274(14.06) 269(35.18) 254(4.82), 240(3.64), 131(15.0) 91(100)
4	352(10.0)	354(1.7, M+2), 351(28.0), 257(93.0), 256(28.5), 255(47.7), 254(28.5) 243(14.9), 242(23.4), 240(31.3), 220(35.5), 132(100.0), 131(38.0)
5f	432(16.9)	433(18.0, M+1), 431(26.0), 271(19.8), 269(20.8), 255(11.2), 254(41.6) 242(100.0), 240(13.3), 132(86.0), 131(10.2), 91(44.6)
5t	[a]	271(3.0), 270(3.0), 269(7.0), 217(11.0), 216(7.0), 215(64.0), 214(71.0), 213(100.0), 184(25.0), 149(30.0), 114(18.0)

a. M^+ Molecular ion not observed.



SCHEME 3

ANTITUMOR TESTING

All the twenty one 2-chloro-5,8,9,13-b-tetrahydro-5-methyl-6*H*-isoquino[2,1-c][1,3,2]benzodiazaphosphorine 6-oxides and sulphides were

tested in the Ehrlich ascites carcinoma screen[15] at several doses. Three of the twenty one test compounds and positive control compound 6-mercaptopurine, exhibited significant inhibition of tumor growth (i.e. tumor growth > 80%) at their optimum dose. Slight activity was noticed below optimum dose for compounds including azetadinyl, pyrrolidinyl and piperazinyl derivatives (**5b-5f**). The chloroethylamino derivative **6** also demonstrated significant antitumor activity in this screen. It should be noted here that in our experience, many compounds, especially alkylating agents appear significantly active in the Ehrlich system as employed (> 85% inhibition). However compounds that have shown activity in other tumor tests (P-388, Walker 256 and L-1210) have often been initially identified by showing complete inhibition in the Ehrlich Test (> 85% inhibition). The Ehrlich system which is known to be immunogenic, not highly discerning, and productive of "misleading results", however, has been dropped by the National Cancer Institute for routine screening.

All the significantly active test compounds in the Ehrlich ascites carcinoma screen possessed an akylating functionality. However, it has been proven that these two features (alkylating function and tetrahydroisoquinoline moiety) did not portray significant activity when compared to Cyclophosphamide (**7**) in this series of compounds, since compounds **4i** and **4j** possess both features and yet are inactive at the dose tested. As expected, aziridinyl ring opening of compound **4a** with HCl gas in absolute ethanol yielded the active 5-[(2-chloroethyl) amino] derivative (**6**). The readily synthesized bis-(2-chloroethyl)amino derivatives **3** and aziridinyl, piperazinyl derivatives were selected for testing against the growth of P-388 lymphocytic Leukemia cells in BDF_1 male mice.[14] These three compounds were tested at multiple doses (Table IV). Compound **3** exhibited the highest activity of these three compounds with a % T/C at 145 at 1(mg/kg)day (% T/C > 125 was considered significant). Compound **5a** exhibited a % T/C of 137 at 10(mg/kg)/day. All the compounds in this series (**5i – 5u**) were tested in this P-388 lymphocytic Leukemia screen at 1(mg/kg)/day, the optimum dose of the active aziridinyl compound **5a**; however, no significant activity was observed for these compounds at these dose. Although the compounds **4** and **5a** exhibited good activity in both the Ehrlich ascites carcinoma screen and the P-388 lymphocytic Leukemia screen, however it should be noted that cyclophosphamide has significantly higher activity than any of the compounds reported. This is in spite of not having the isoquinoline moiety, thereby suggesting that this series of compounds may not encourage further antitumor exploration.

TABLE IV Antitumor activity of 2-chloro-5,8,9,13b-tetrahydro-5-methyl-6*H*-isoquino[2,1-c][1,3,2]benzodiazaphosphorine 6-oxides and silphides in BDF_1 Mice Bearing Lymphocytic Leukemia P-388

Compound (N=5)[a]	*dose*[b] *(mg/kg)/day*	*av days survival*[c]	*% T/C*[d]
3	0.5	10.5/9.2	114
	1.0	13.3/9.2	145
	2.0	12.6/9.2	137
	3.0	10.2/9.2	111
	5.0	11.0/9.2	120
	10.0		Toxic
5a	0.5	10.5/9.2	114
	1.0	11.0/9.2	120
	5.0	10.9/9.2	118
	10.0	12.6/9.2	137
	12.0	9.0/9.2	98
5b	1.0	10.2/9.2	111
	5.0	9.4/9.2	102
	10.0	9.2/9.0	102
	20.0	8.0/9.2	87
6	1.0	10.2	111
5j	30.0	3.0/9.2	33
Reference: Cyclophosphamide	6.5	10.2/9.2	339
	1.0	13.0/9.2	143

a. N = number of mice per test group
b. 0.05% Tween 80 was used as vehicle for test compounds and control.
c. Average days survived for treated/average days survived for control.
d. % T/C > 125 is considered significantly active.. No significant weight loss Vs control was observed for animals in this experiment.

EXPERIMENTAL SECTION

Melting points were determined on a Mel-Temp apparatus, Laboratory devices, Cambridge, Mass, USA and are uncorrected. The elemental anal-

ysis were performed at the Regional Sophisticated Instrumentation Centre, Central Drug Research Institute (RSIC-CDRI), Lucknow, India and were within the ±0.4% of theoretical values. Precoated TLC Plates (5 × 10 cm) of silica gel 60F-254 (layer thickness 0.25 mm) from Aldrich Chemical company were used for TLC analysis and the spots were detected with a Mineralight (UV, shortwave). Column chromatography was accomplished with silica gel 60 (70–230 mesh ASTM) from Aldrich Chemical Company, USA. Infrared spectra were obtained from a Perkin Elmer Pe 781 spectrophotometer. Routine proton nuclear magnetic resonance (^{1}H NMR) were obtained on a Varian EM-390 and FX 100 MHz (Jeol Ltd). In all ^{1}H NMR spectra, tetramethyl silane was used as "internal reference" for determining chemical shifts on the δ scale. The abbreviation used in the descriptions of the NMR spectra are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. All solvents were reagents grade and 1-(o-amino phenyl)-1,2,3,4-tetrahydroisoquinoline and bis(2-chloroethyl)-phosphoramidic dichloride were procured from Aldrich Chemical Company, USA and were used without further purification. Mass spectra was obtained from CDRI Lucknow India. The mass spectra was recorded on a Jeol JMS-D 300 with JMA-2000 data processing unit at 70 eV and at a trap current of 100 μA; and also a Finnigan 4610 instrument operating at 80 eV at the University of Vermont, Vermont USA. Antitumor line screen was performed at the National Cancer Institute, NCI, National Institute of Health, NIH Bethesda, Maryland, USA.

Aryloxyphosphoro(thio)dichloridates[17–19]

Equimolar quantities of the substituted phenols/8-hydroxyquinoline and phosphorus oxychloride were reacted in dry benzene employing triethylamine to scavenge the liberated hydrogen chloride gas. The reaction mixture was refluxed and vigorously stirred for 10–14 hr. The dark brown liquid and sometimes solid obtained after working up the reaction was subjected to fractional distillation and/or recrystallization.

2-Chloro-6-[bis(2-chloroethyl)amino]-5,8,9,13b-tetrahydro-5-methyl-6H -isoquino [2,1-c][1,3,2]benzodiazaphophorine 6-oxides (3)

A solution of 2.59g (0.01 mole) of bis(2-chloroethyl)phosphoramidic dichloride in 25ml of dry benzene was added drop wise over a period of 30 min to a cold (-5°) and stirred solution of 2.72g (0.01 mole) of

1-[5-chloro-2-(methylamino)phenyl]-1,2,3,4-tetrahydroisoquinoline (**1**) and 2.2 g (0.02 moles) of triethylamine in 50ml of dry benzene. The reaction mixture was stirred slowly from −5° to room temperature, and was later refluxed for 5 hr. The progress of the reaction was followed by TLC. On working up the reaction, 3.1 g (69%) of **3** was obtained as pale yellow amorphous solid melting at 105–107°.

2,6-Dichloro-5,8,9,13b-tetrahydro-5-methyl-6H-isoquino [2,1-c][1,3,2]-benzodiaza phosphorine 6-sulphide (4)

A solution of 1.83 g (0.01 mole) of thiophosphorylchloride in 25ml of dry benzene was added drop wise for over a period of 30 min to a cold solution of 2.72 g (0.1 mole) of compound **1** and 2.02 g (0.02 mole) of triethylamine in 50ml of dry benzene. After the addition, the reaction mixture was slowly brought to mild refluxing for 3 hr. The progress of the reaction was monitored by TLC. On working up the reaction, the crude product obtained was purified by chromatography over a column of silica gel and eluting with a mixture of benzene-light petroleum (3:1) to give **4** as colorless solid. Yield 2.0 g (55%); m.p. 78–80°.

2-Chloro-6-(cyclicamino)-5,8,9,13b-tetrahydro-5-methyl-6H-isoquino [2,1-c][1,3,2] benzodiazaphosphorine 6-sulphides (5a-5l)

Equimolar quantities (0.01 moles) of compound **4** and various cyclic amines were reacted in dry benzene and stirred for 30 min at 5°. The crude products obtained were purified by chromatography over a column of silica gel and eluting with benzene-ethylacetate (4:1) mixture. Good yields were obtained (>52%) and m.p. varied from 76–125°.

2-Chloro-6-(8-hydroxyquinolinyl/(thio)phenoxy-,5,8,9,13b-tetrahydro-5-methyl isoquino[2,1-c][1,3,2]benzodiazaphosphorine 6-oxides (5m-5u)

Equimolar quantities (0.01 mole) of compounds **1** and aryloxyphosphorodichloridates were treated with 2.2 g (0.2 moles) of triethylamine, in dry benzene at 5° and stirred for 2 hr. The course of the reaction was monitored by TLC. On working up the reaction, the crude product (**5m-5u**) were purified by column chromatography. Low yields were obtained (<40% except for **5r** and **5t**) and melting points varied between 121 to 147°.

2-Chloro-6-(2-chloroethylamino)-5,8,9,13b-tetrahydro-5-methyl-6H-isoquino[2,1-c][1,3,2]benzodiazaphosphorine 6-sulphides (6)

1.9 g (0.005 mole) of 5a was dissolved in 25 ml absolute methanol in a continuously stirred sealed two necked flask and HCl gas was passed through the solution for 45 min. TLC indicated two spots with r_f values corresponding to **5a** and **6**. On working up the reaction, **6** was isolated and purified by column chromatography on silica gel and eluting with pet-ether-benzene (2:1) giving 0.71 g (35%); and m.p. 116–118°.

Methods of Antitumor Testing

Test compounds were homogenized in 0.5% poly(oxyethylene) sorbitan monooleate (i.e. Tween 80) or 5% absolute ethanol, USP in a 0.05% tween 80 solution (1 ml of absolute EtOH in 19 ml of 0.05% Tween). The 5% absolute EtOH Tween 80 was used as a vehicle to improve compounds solubility. Compounds solution were administered intra-peritoneally (ip).

Ehrlich Ascites Carcinoma Screen[15]

Male CF_1 mice (22–25 g) were injected ip with 2 × 106 Ehrlich carcinoma cells on day 0. Injectible solutions of the test compounds were administered ip on days 1 through 8. Mice were sacrificed on day 9. In each test group, the ascites fluid volume per mouse and the ascrit (packed cell volume) were determined[15]. Results were expressed as % inhibition of tumor cell growth as calculated according to the following equation:

$$\frac{\%\text{ inhibition of}}{\text{tumor growth}} = 100 \times \frac{(\text{Vol.of treated})(\text{Ascrit of treated})}{(\text{Vol. of control})(\text{Ascrit of control})}$$

6-mercaptopurine was used as the positive control compound. An inhibition of tumor growth, greater than 80% was considered significant.

P-388 Lymphocytic Leukemia Screen

On day 0, male BDF_1 mice (20–23 g) were injected ip with 1 × 106 P-388 lymphocytic leukemia cells as described in the NIH protocol 1.2[16] Injectible solutions of the test compounds were administered ip one daily on days 1 through 14[15] (instead of day 1–9 as described in the NIH protocol). Cyclophosphamide (Cytoxan) was used as the positive control compound.

Five mice per test group were used and % T/C values greater than 125 were considered significantly active.

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