The Antineoplastic Activity of 2,2,4,4-Tetrakis(aziridinyl)-6,6,-dichlorocyclotriphosphaza-1,3,5-triene, gem-$N_3P_3Az_4Cl_2$, a Novel Anticancer Agent

GUY GUERCH*, JEAN-FRANCOIS LABARRE, FRANCOIS SOURNIES

Laboratoire Structure et Vie, Université Paul Sabatier, 118, Route de Narbonne, 31062 Toulouse Cedex, France

MICHEL MANFAIT

Laboratoire de Recherches Optiques, Université de Reims, Moulin de la Housse, 51062 Rheims Cedex, France

FEDERICO SPREAFICO and STEFANIA FILIPPESCHI

Istituto di Ricerche Farmacologiche 'Mario Negri', Via Eritrea 62, 20157 Milan, Italy

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Synthesis, Mass spectrum, N.M.R., IR and Raman data as well as X-Ray crystal structure of a new anticancer cyclophosphazene, namely gem-$N_3P_3Az_4Cl_2$ (Az = Aziridinyl), are described. Antitumor activity in vivo *of this chemical on 5 rodent tumors was found comparable to the ones of $N_3P_3Az_6$ (MYKO 63) and $N_3P_2SOAz_5$ (SOAz). In view of its activity, gem-$N_3P_3Az_4Cl_2$ constitutes a starting material for the synthesis of intramolecular combinations with (N–H)-bearing antitumor drugs (which may possess synergic activities).*

Introduction

Interest in Inorganic Ring Systems as anticancer drugs, initially mentioned by Cernov *et al.* [1], has recently been enhanced by the finding that the aziridinocyclophosphazenes $N_3P_3Az_6$ and $N_4P_4Az_8$ (Az = Aziridinyl) were active on a large series of experimental neoplasms [2–4]. In subsequent studies conducted with the E.O.R.T.C. Screening and Pharmacology Group, and employing a range of rodent neoplasms including leukemias and solid tumors of different histological nature, growth rate and chemotherapeutic sensitivity, $N_3P_3Az_6$ (code name MYKO 63) was found to be the more active of the two chemicals.

In order to further explore the potential of this novel class of antitumorals, a new series of chemicals was prepared. Following the approach of adding methyl groups on the 2 and 2′ C positions of the aziridino ligands of $N_3P_3Az_6$ led to $N_3P_3(MeAz)_6$, which has been shown to display an activity essentially comparable to that of MYKO 63 [5]. In a second approach, P atoms of the N_3P_3 ring have been replaced stepwise by S atoms, giving a series of $(NPAz_2)_2(NSOX)$ derivatives: at least 3 of such derivatives (*i.e.* SOF, in which X = F; SOPH1, in which X = Ph and SOAz, in which X = Az) have revealed potent antineoplastic activity [6–8].

In view of the fact that SOAz, the most active compound of the latter series, was non-mutagenic for various bacterial systems and showed in preliminary tests in dogs and monkeys no significant nephro-hepato-, or cardiotoxicity and little hematotoxicity, it was of interest to explore the biological activity of additional molecules.

This contribution deals with an investigation of the chemical, physico-chemical and biological properties of a dichlorinated derivative of MYKO 63, gem-$N_3P_3Az_4Cl_2$. Aziridinolysis of $N_3P_3Cl_6$ occuring indeed through a definite geminal pattern [9], this chemical was originally prepared as a starting material for the synthesis of further intramolecular combinations with (N–H)-bearing antitumor drugs through HCl elimination with the aim of searching for synergic activities.

Synthesis and Purity

The synthesis of the chemical was performed following the processes described both by Kobayashi *et al.* [10] and by Rätz *et al.* [11]. The melting point of the sample obtained was 129.5 °C in agreement with previous data: 128–129 °C [10], 131 °C [11] and 129–130 °C [12].

*Author to whom correspondence should be addressed.

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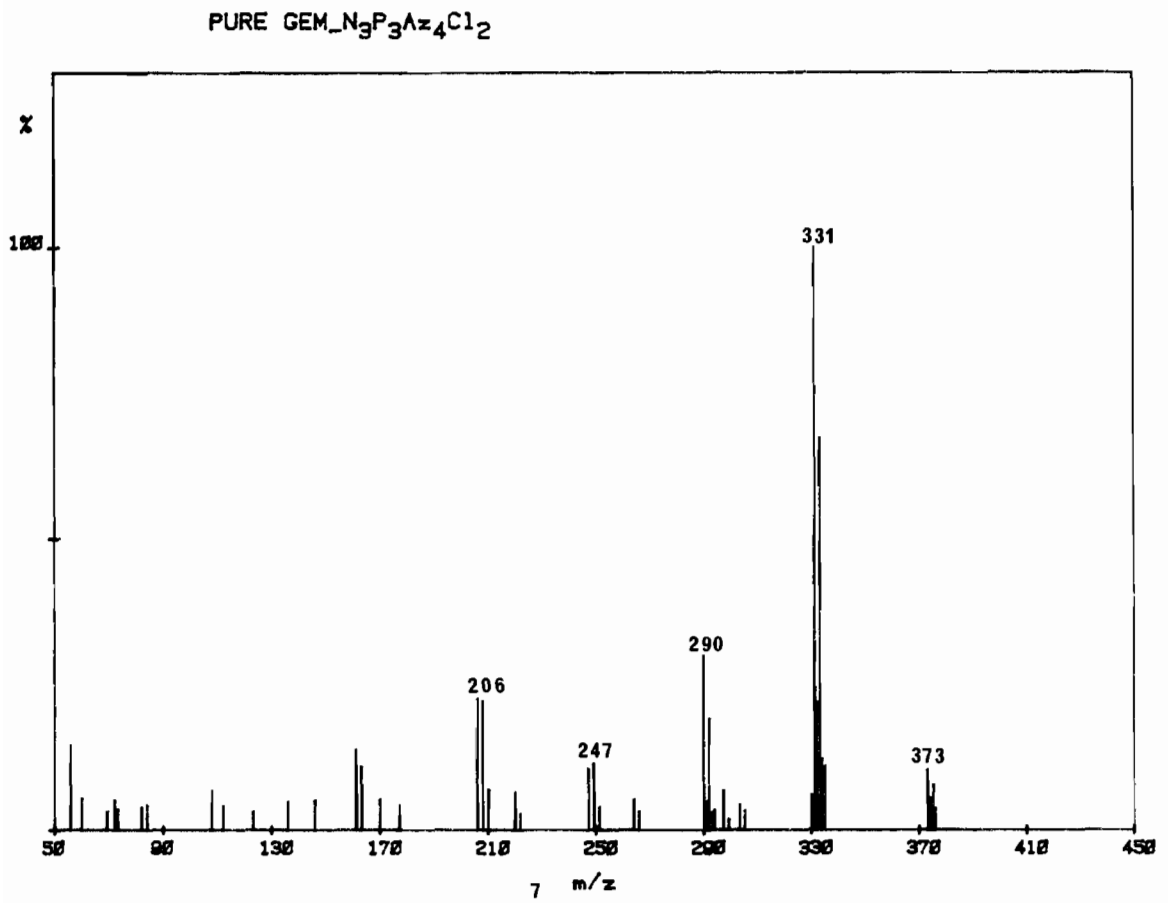

Fig. 1. Mass spectrum of pure gem-$N_3P_3Az_4Cl_2$ (M.P. 129.5 °C).

Mass Spectrometry

The spectra were recorded on a R1010 Ribermag quadrupole mass spectrometer, using a direct inlet system. The source temperature was 150 °C, electron energy 70 eV. The spectra were recorded by means of a DEC PDP 8/M computer and stored on disk. About 1 μg of sample was introduced into the probe. The probe temperature was then slowly and continuously increased from ambient temperature to 100 °C, taking care that neither the electron multiplier nor the amplifier were in a saturated condition at any time. The area of the curves corresponding to the current carried by the selected ions were calculated by the computer.

The 70 eV electron impact mass spectrum of the 129.5 °C sample is presented in Fig. 1. The molecular ion is observed at m/z 373 (10.3%) with a set of satellites at m/z 374 (5.4%), 375 (7.7%), 376 (3.7%) and 377 (1.4%). The intensity ratio between these five peaks indicates the presence of two chlorine atoms in the molecule. One main fragmentation route is detected: an aziridino radical (42 mass units) is expelled giving the base peak at m/z 331 (100%). Further consecutive losses of the aziridino substituents are associated with H-transfers. Thus, the loss of 41 mass units (C_2H_3N = Az minus H) produces the ion at m/z 290 or, alternatively, the expulsion of an aziridine molecule (43 mass units) from m/z 290 gives the ion at m/z 247. The elimination of a third substituent gives the ion at m/z 206 and 208.

From the simplicity of this spectrum, it is quite easy to detect the superimposition of peaks due to possible contaminants. It was possible in this way to observe clearly that the crude material (*i.e.*, before any recrystallization from suitable benzene-hexane mixtures) contains actually a small but significant amount of $N_3P_3Az_5Cl$ as an impurity. Figure 2 proves how easy is the detection of the impurity.

In the high mass range we observe peaks at m/z 380 (1.8%) and 382 (1.0%), the intensity ratio between them indicating the presence of one chlorine atom only in the impurity. The largest doublet at m/z 338 (14.0%) (base peak) and 340 (5.3%) arises from the loss of an aziridino radical (42 mass units). The two peaks at m/z 254 (8.3%) and 256 (3.8%)

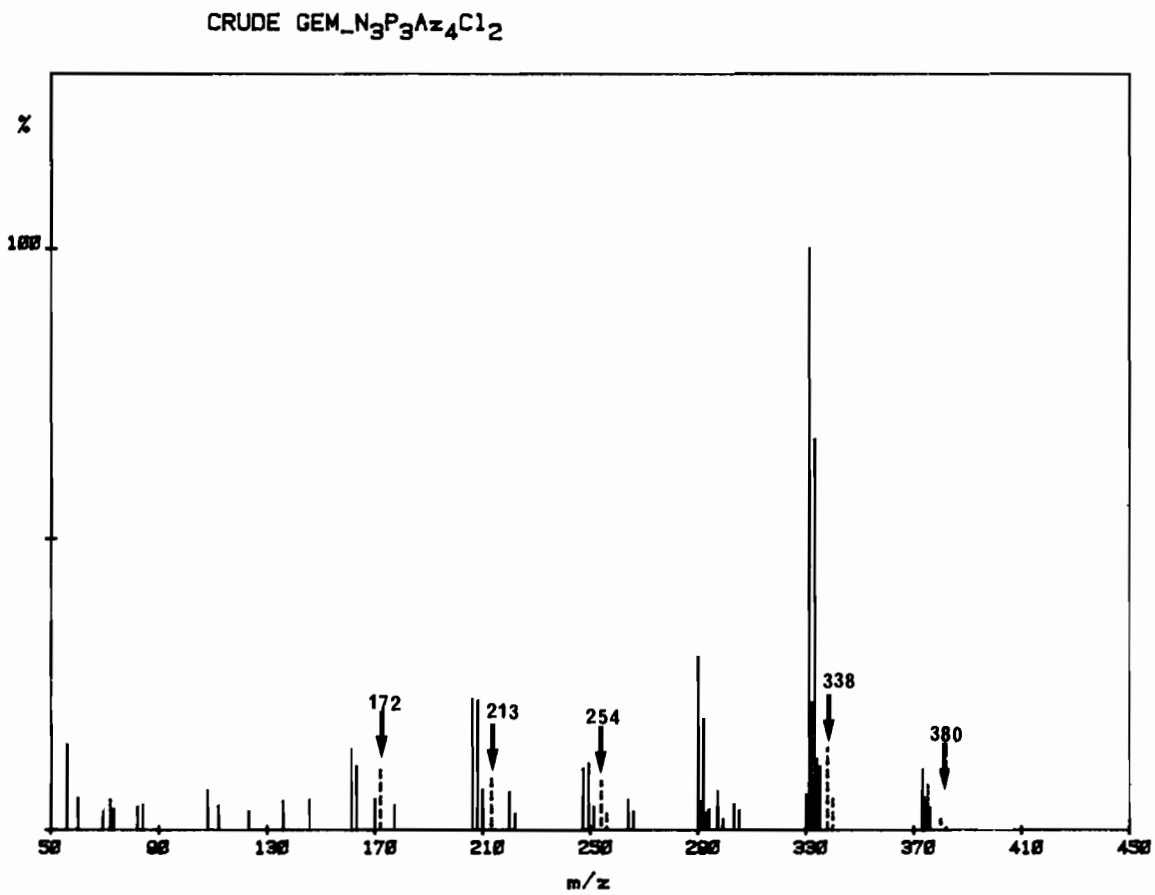

Fig. 2. Mass spectrum of crude gem-$N_3P_3Az_4Cl_2$ containing traces of $N_3P_3Az_5Cl$.

indicate the loss of a second substituent associated with H-transfer. Then, m/z 213 (8.9%) arises from loss of third aziridino substituent and m/z 172 (10.5%) from loss of fourth ligand as an aziridine molecule (43 mass units). Further elimination gives less characteristic peaks.

The impurity in the crude sample of gem-$N_3P_3Az_4Cl_2$ is definitely 2,2,4,4,6-pentakis(azirıdinyl)-6-monochlorocyclotriphosphaza-1,3,5-triene, $N_3P_3Az_5Cl$.

Incidentally, thin-layer chromatography (TLC) gives the following R_F values (CH_2Cl_2 50% plus Et_2O 50%): 0.40 and 0.08 for $N_3P_3Az_4Cl_2$ and $N_3P_3Az_5Cl$ respectively.

Thus, mass spectrometry appears to be an adequate tool for controlling the purity of $N_3P_3Az_4Cl_2$ in an unambiguous way, as was demonstrated previously in the case of other cyclophosphazenes for biological use [13].

NMR Spectroscopy

The ^{31}P NMR spectrum of pure gem-$N_3P_3Az_4Cl_2$ was recorded (Fig. 3) on a Brucker WH 90 instrument. The doublet at 35.9 and 35.2 ppm corresponds to the PAz_2 entities and the triplet around 25.1 ppm at the PCl_2 moieties (intensity ratio 2:1). These data are consistent with very accurate ones which were recently reported [7] for other aziridino- and aminochlorocyclotriphosphazenes (Table I).

TABLE I. ^{31}P NMR Data of Some Azirıdino Derivatives of $N_3P_3Cl_6$; Chemical Shifts (in ppm *versus* 85% H_3PO_4) are defined as Positive in Low Field Direction.

Compound	Chemical Shift		Reference
	PCl_2	PAz_2	
$N_3P_3Cl_6$	19.9		[7]
$N_3P_3Az_4Cl_2$	25.1	35.2	This study
$N_3P_3Az_5Cl$		37.2	[7]
$N_3P_3Az_6$		37.6	[6]

Infrared Spectroscopy

The infrared spectrum (KBr disks) was recorded at room temperature on a Perkin-Elmer 237 spectro-

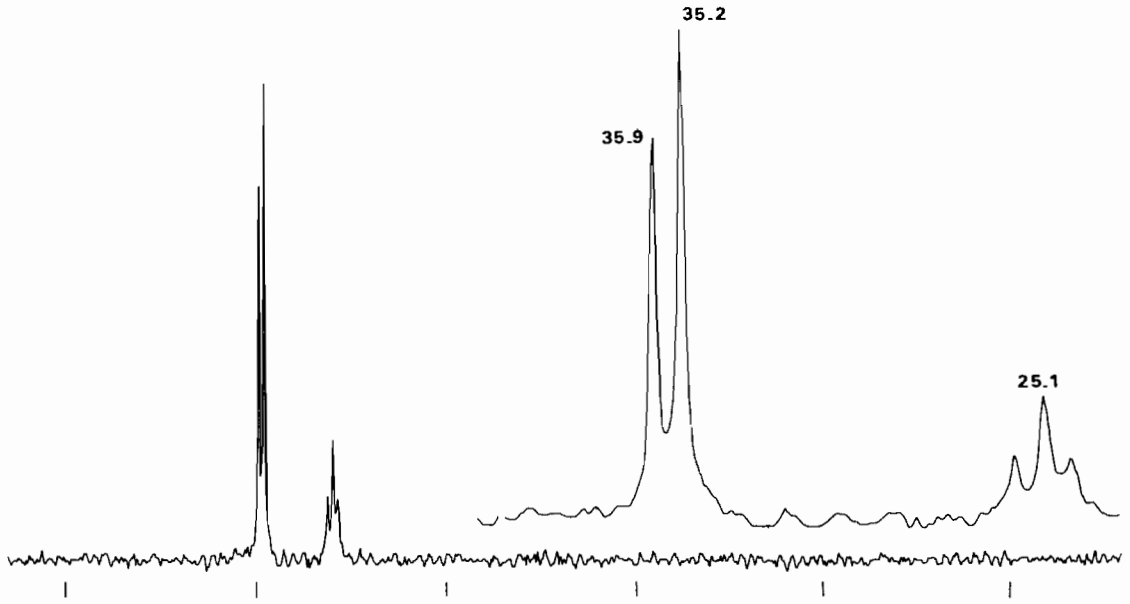

Fig. 3. ^{31}P NMR spectrum of pure gem-$N_3P_3Az_4Cl_2$.

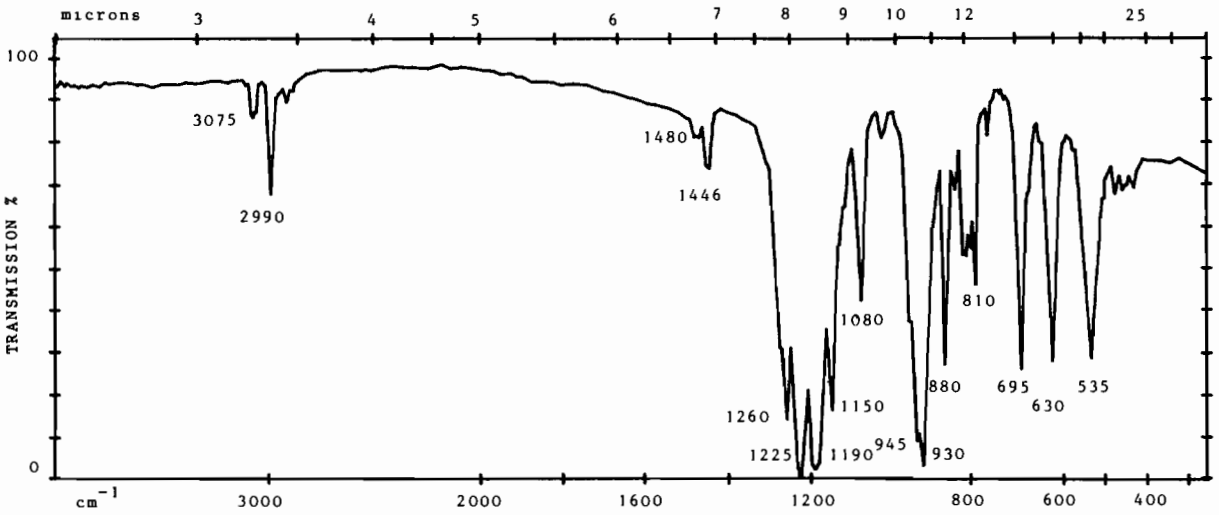

Fig. 4. IR spectrum of pure gem-$N_3P_3Az_4Cl_2$.

meter (range 4000–200 cm^{-1}, calibration with polystyrene lines) (Fig. 4). This spectrum was assigned (Table II) by comparison with previous data from our own work [14].

Raman Spectroscopy

Raman spectrum of solid (powder) $N_3P_3Az_4Cl_2$ was recorded on a Coderg T800 spectrometer equipped with a Coherent Radiation Model 52B Ar^+ laser using 400 mW of power from the 488.0 nm line and a cooled EMI 9558 QB photomultiplier for detection. The T800 spectrometer was driven by an Alcyane computer (MBC, France).

The spectrum (Fig. 5) was recorded with a slit width of 4 cm^{-1}. The Raman frequencies reported here (Table III) are accurate to ±2 cm^{-1}. Assignments were performed from spectroscopic data previously obtained for $N_3P_3Az_6$ [14].

X-ray Crystal and Molecular Structures

The molecular structure of the title compound was determined on a CAD-4 ENRAF-NONIUS PDP 8/M computer-controlled single crystal diffractometer by Galy and Enjalbert. The whole description of the

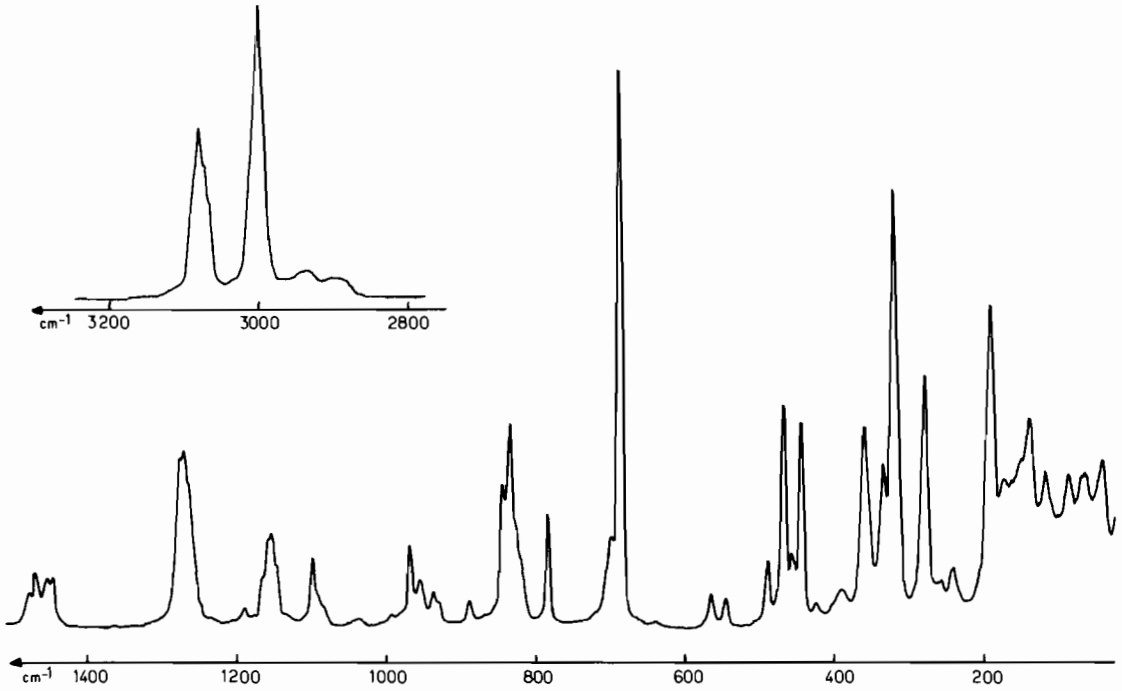

Fig. 5. Raman spectrum of pure gem-$N_3P_3Az_4Cl_2$.

TABLE II. IR Vibrational Frequencies of gem-$N_3P_3Az_4Cl_2$ (solid state).

Frequency	Assignment
490 w	$\rho_w(NC_2)$ + PN_{exo} (IP deformation)
535 s	$\nu_s(PCl)$
630 s	$\nu_{as}(PCl) + \nu_{as}(PAz_2) + \rho_{w,s}(PAz_2)$
695 s	Ring deformation IP, $\delta_s(NPN)$
780 w	Ring breathing, $\nu_s(PN)$
810 m, 832 w, 840 m	Ring deformation IP, $\delta_s(NC_2)$ + $\rho_{r,s}(CH_2) + \rho_{r,as}(CH_2)$
880 s	$\nu_s(PN)$
930 s, 945 s, 960 m	$\rho_{w,s}(CH_2)$
1037 vw	$\nu_{as}(PN)$
1080 m	$\rho_{\tau,s}(CH_2)$
1120 vw, 1150 s	$\rho_{w,as}(CH_2) + \nu_{as}(PN)$
1190 vs, 1225 vs	$\nu_{as}(PN) + \rho_{\tau,as}(CH_2)$
1260 s	$\nu_{as}(NC_2)$
1446 w	$\delta_{as}(CH_2)$
1480 vw	$\delta_s(CH_2)$
2990 w	$\nu_{as}(CH)$
3075 vw	$\nu_s(CH)$

TABLE III. Raman Vibrational Frequencies of gem-$N_3P_3Az_4Cl_2$ (solid state).[a]

Frequency	Assignment
40, 63, 70, 85	Ring deformation OP (torsion)
117	
139 w	
151	
173	
192 m	$\rho_r(PCl_2)$
240	
259	
281 m	
321 s	$\nu_s(PAz_2)$
335 w	
361 w	$\nu_s(PCl_2)$
389	
423	
444 w, 457, 469 m, 489	$\nu_s(PAz_2)$ + Ring deformation IP, $\delta_{as}(NPN)$
544, 564	$\nu_s(PCl_2) + \nu_{as}(PCl_2)$

(continued overleaf)

TABLE III. *(continued)*

Frequency	Assignment
636	
687 vs	Ring deformation IP, δ_s(NPN)
699	
783 w	Ring breathing, ν_s(PN)
820 sh	$\rho_{r,s}(CH_2) + \rho_{r,as}(CH_2)$
824 sh	
834 m	Ring deformation IP, $\delta_s(NC_2)$
843	
866	
888	ν_s(PN)
929 sh	$\rho_{\omega,s}(CH_2)$
937	
954	
968 w	
992	
1037	ν_{as}(PN)
1082 sh	$\rho_{\tau,s}(CH_2)$
1097	
1132	$\rho_{\omega,as}(CH_2) + \nu_{as}$(PN)
1147 sh	
1153 w	
1166 sh	
1189	
1234	
1262 sh	
1272 m	Ring breathing Az, $\nu_s(NC_2)$
1444	$\delta_{as}(CH_2)$
1453	
1469	$\delta_s(CH_2)$
1478 sh	
2891	ν_{as}(CH)
2928	
2930	
3000 s	
3063 sh	ν_s(CH)
3070sh	
3077 w	

[a]All observed frequencies are in cm^{-1}. Abbreviations used are: s, strong; m, medium; w, weak; v, very; sh, shoulder; IP, in local plane; OP out-of-local plane; ρ_τ = twist; ρ_ω = wagg; ρ_r = rock; δ = scissor; τ = torsion; Az = aziridino (NC_2H_4).

structure, including bond-lengths, valence and torsional angles, will be published elsewhere [15].

The molecular pattern so obtained, visualized in Fig. 6, calls for the following remarks. (*i*) The exocyclic nitrogen atoms have a definite pyramidal

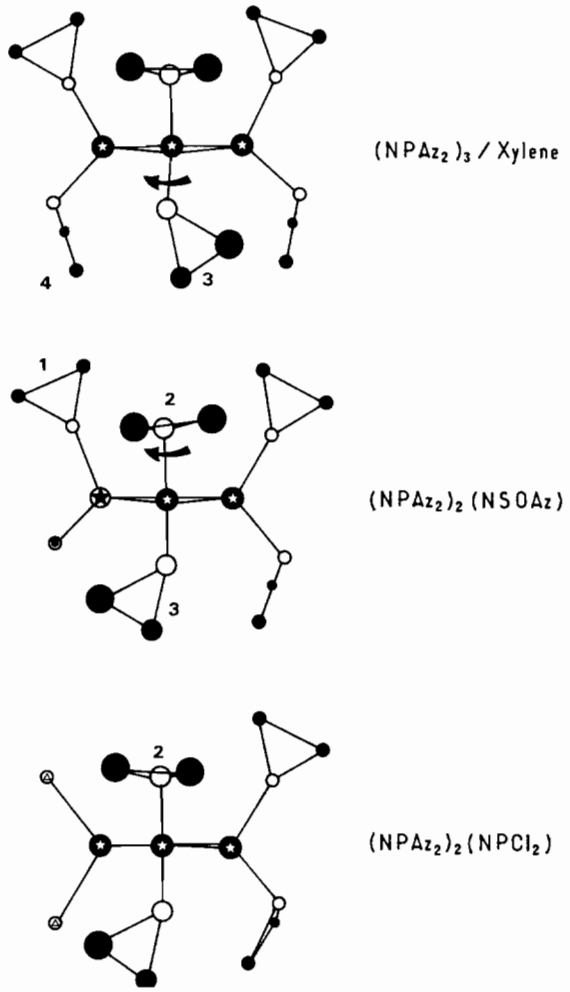

Fig. 6. Molecular patterns of MYKO 63, $(NPAz_2)_3$, SOAZ 2A, $(NPAz_2)_2(NSOAz)$, and gem-$N_3P_3Az_4Cl_2$, $(NPAz_2)_2(NPCl_2)$: ●· P, ⊛: S, ○· N, •, C, ◬: Cl.

character as in other related derivatives, namely $(NPAz_2)_3$ (MYKO 63) and $(NPAz_2)_2(NSOAz)$ (SOAz). Several X-Ray analyses had been performed on these two molecules, and the pyramidal character of N_{exo} atoms was systematically observed either in unsolvated [16, 17] or in clathrate [18–21] structures. (*ii*) This pyramidal character *remains strictly the same* through the series no matter which atom (P or S) the aziridinyl 'wing' is grafted on. In other words, the distance of any N_{exo} to the corresponding PCC or SCC plane stays equal to 0.69 ± 0.02 Å (Fig. 7). Thus, the various spatial arrangements which are observed for these wings from one structure to the other may proceed from a common conformational analysis. Such an analysis was achieved by Lahana [22, 23] in terms of steric hindrances and internal rotational barriers, and Fig. 6 visualizes the resemblances of the structure of $(NPAz_2)_2(NPCl_2)$

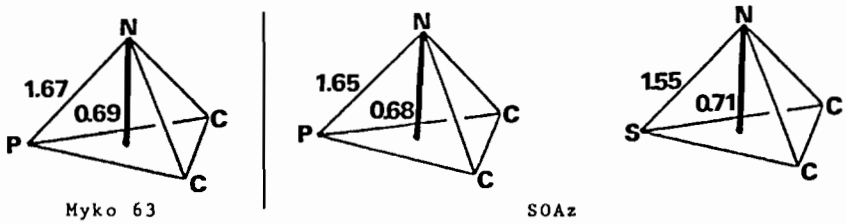

Fig. 7. Pyramidal character of N_{exo} atoms in MYKO 63 and SOAz.

with MYKO 63 when crystallized from *m*-xylene [16] and with one of the three allotropic varieties, Namely SOAz 2A, from SOAz [17]. When passing from SOAz to $(NPAz_2)_2(NPCl_2)$, wing 2 rotates gently by about 8° towards the free space left vacant by the replacement of wing 1 by a chlorine atom. The rest of the structure remains practically unchanged upon this replacement. Incidentally, a similar rotational re-arrangement is observed when passing from MYKO 63 to SOAz, wing 3 rotating by about 120° towards the free space left by the replacement of wing 4 by an oxygen atom.

Thus, the X-Ray molecular structure of $(NPAz_2)_2$-$(NPCl_2)$ is consistent with the rules stated by Lahana for predicting the preferred conformations of aziridinyl-bearing inorganic ring systems [22, 23].

Antitumor Activity

Experimental Conditions

For the tests on the L1210 and P388 leukemias, 10^5 and 10^6 cells respectively were transplanted intraperitoneally (i.p.) on day 0 in compatible CD2F1 male mice (20 ± 2 grams), the drug treatment being initiated 24 h later. Male CD2F1 mice were also used as recipients for the compatible line 26 colon carcinoma (inoculum being 10^6 cells i.m.) and P815 mastocytoma (10^6 cells i.p.), whereas the line 16 mammary carcinoma (5×10^5 cells i.m.) was transplanted in compatible B6C3F1 hosts. The drug was always dissolved in sterile saline and administered i.p., and at least 10 animals per group were used. Results presented are representative of at least two experiments performed. For solid tumors, diameters were taken with Vernier calipers by two independent observers and results averaged. As a further evaluation criterion, the percent increase in median lifespan over untreated controls (T/C%) was also calculated [24].

Results

As shown in Table IV, when single well-tolerated doses of the title compound were administered to L1210 and P388 leukemia-bearing mice, a significant and dose-dependent antitumoral effect was observed,

TABLE IV. Antitumor Activity (T/C%) of gem-$N_3P_3Az_4Cl_2$ Against P388[a] and L1210[b] Leukemias (CD2F1 Male Mice).

	P388	L1210
Dose (mg/Kg/i.p.) Once, Day 1		
12	136	115
18	152	146
24	168	140
Days 1, 5 and 9		
4	–	106
6	145	–
8	–	112
12	170	118
16	–	125
20	–	186
24	151	–

[a] 10^6 cells i.p. on day 0. [b] 10^5 cells i.p. on day 0.

the effect being markedly increased when a repeated injection treatment schedule was employed. In fact, approximately doubled lifespans were seen in both systems with doses of 16–20 mg/Kg × 3, the highest non-lethal dose (LD_o) for this drug being 24 mg/Kg in CD2F1 mice.

The interesting potential as an anti-neoplastic agent of the title compound is supported by the findings presented in Tables V to VII, which show the activity of gem-$N_3P_3Az_4Cl_2$ on line 16 mammary and line 26 colon carcinomas and P815 mastocytoma. It may be seen that in each of these 3 model systems (comprising poorly responsive, slow-growing tumors) a repeated injection schedule was associated with significant retardations in primary tumor growth and clear increases in lifespan.

Conclusion

From the data presented, we may conclude as follows. (*i*) the antitumor activity against P388 and L1210 leukemias, line 16 mammary and

TABLE V. Effects of gem-$N_3P_3Az_4Cl_2$ on Line 16 Mammary Carcinoma[a] in B6C3F1 Mice.

Exp. group	Dose mg/Kg i.p.	Average tumor diameters (cm ± S.E.) on days										T/C%
		15	18	21	25	29	33	36	40	53	59	
Controls	–	0.77 ± 0.03	1.03 ± 0.05	1.3 ± 0.08	1.69 ± 0.09	1.83 ± 0.2	2.15 ± 0.05	2.3 ± 0.03	–	–	–	
Drug	20	–	–	–	toxic	toxic	–	–	–	–	–	35
	15	–	–	–	–	–	–	–	–	–	0.95 ± 0.05	128
	10	–	–	–	–	–	–	–	0.6 ± 0.1	1.6 ± 0.09	2.16 ± 0.13	168
	5	–	–	–	0.75 ± 0.1	0.85 ± 0.13	0.89 ± 0.13	1.1 ± 0.1	1.17 ± 0.18	1.57 ± 0.32	–	172

[a] 5×10^5 cells were implanted i.m. on day 0, and drug administered from day 1 to day 9, once a day.

TABLE VI. Effects of gem-$N_3P_3Az_4Cl_2$ on Line 26 Colon Carcinoma[a] in CD2F1 Mice.

Exp. group	Dose (mg/Kg/i.p.)	Average tumor diameters (cm ± S.E.) on days							T/C%
		7	12	18	21	25	29	33	
Controls	–	0.59 ± 0.03	1.22 ± 0.03	1.26 ± 0.03	1.47 ± 0.07	1.75 ± 0.15	–	–	
Drug	20	–	–	toxic	toxic	–	–	–	62
	15	–	–	toxic	toxic	–	–	-	98
	10	–	0.6 ± 0.1	0.67 ± 0.11	0.88 ± 0.09	1.09 ± 0.08	1.24 ± 0.1	1.71 ± 0.11	173
	5	0.51 ± 0.01	0.96 ± 0.08	1.07 ± 0.07	1.29 ± 0.06	1.47 ± 0.09	1.6 ± 0.09	1.9 ± 0.2	128

[a] 10^6 cells were implanted i.m. on day 0 and drug administered from day 1 to day 9, once a day.

TABLE VII. Effects of gem-$N_3P_3Az_4Cl_2$ on P815 Mastocytoma[a] in CD2F1 Mice.

Exp. group	Dose (mg/Kg/i.p.)	Schedule	MST (days ± S.E.)	T/C%
Controls	–	–	10.6 ± 0.2	–
Drug	30	Day 1	12.5 ± 2.7	117
	24	Day 1	16.8 ± 0.4	158
	20	Day 1	16.3 ± 1.6	153
	18	Day 1	15.3 ± 1.0	144
	12	Day 1	16.0 ± 1.3	150
	10	Day 1	13.5 ± 1.2	127
Drug	24	Days 1, 5 and 9	18.7 ± 2.3	176
	20	Days 1, 5 and 9	18.0 ± 0.6	169
	16	Days 1, 5 and 9	18.7 ± 0.6	176
	12	Days 1, 5 and 9	17.8 ± 0.6	167
	8	Days 1, 5 and 9	15.3 ± 1.3	144

[a] 10^6 cells i.p. on day 0.

line 26 colon carcinomas and P815 mastocytoma is not dramatically altered when passing from MYKO 63 [3, 4] and SOAz [25] to gem-$N_3P_3Az_4Cl_2$, (*ii*) thus, the latter molecule may constitute a starting material for the synthesis of intramolecular combinations with (N–H)-bearing antitumor drugs through HCl elimination. The syntheses of such combinations – with the aim of searching for synergic antineoplastic activities – are now in progress in our laboratory.

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