STUDIES ON POTENTIAL ANTITUMOR AGENTS (III).
Synthesis of 4-Arylcyclophosphamides.

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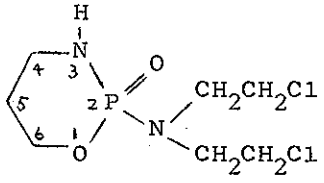
Nine cis-trans pairs of 4-arylcyclophosphamides have been synthesized from benzaldehydes in three steps. Structures were assigned based on infrared spectra.

Cyclophosphamide, 2-bis(2-chloroethyl)aminotetrahydro-2H-1,3,2-oxazaphosphorinane 2-oxide (I), is an antitumor agent now used in the treatment of various kinds of human cancer. The mechanism of action has been well studied in recent years. It has been shown that the in vivo degradation of this alkylating agent involved, as the first step, oxidation at the C-4 position on the 1,3,2-oxazaphosphorinane ring.[1-3]



I

This synthetic study concerns structural modification at the C-4 position. An aryl group at this position is expected, from the electronic point of view, to facilitate the oxidation and thus to modify its pharmacological activity, although the steric consideration would predict retarded oxidation.

4-Arylcyclophosphamides (cpds. 20-28) have now been synthesized starting from benzaldehydes. The aldehydes were condensed with equimolar amounts of malonic acid in refluxing ethanol in the presence of two mole equivalents of ammonium acetate to form 3-aryl-3-aminopropionic acids[4] (cpds.1-9) in 32.1-96.7% yields (Table I).

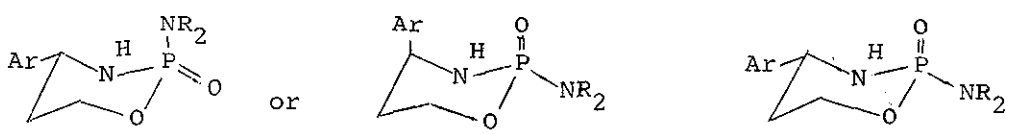
The amino acids were then reduced with 2.5 mole equivalents of lithium aluminum hydride in refluxing dry tetrahydrofuran to form 3-aryl-3-aminopropanols[5] (cpds. 10-18) in high yields (61.1-97.0%)(Table II).

Bis(2-chloroethyl)phosphoramidic dichloride (cpd. 19) was prepared by the reaction of phosphorus oxychloride with bis(2-chloroethyl)amine hydrochloride by the known procedure.[6]

The nine amino alcohols (cpds. 10-18) were allowed to react at room temperature with equimolar amounts of cpd. 19 in the presence of 2 mole equivalents of triethylamine in ethyl acetate.[7] The reaction mixture was stirred for 48 hours, and filtered to remove triethylamine hydrochloride. The clear solution was rotary evaporated and the residue was chromatographed on silica

gel, eluting with benzene containing 5-15% ethyl acetate. Two isomers (fast migrating A and slow migrating B according to their relative mobilities on column chromatography) were obtained in nearly equal amounts in each case. The two isomers in each pair have the same mass spectra but different crystalline forms, mp, infrared spectra, and proton nmr spectra. Relevent data were shown in Table III and IV.

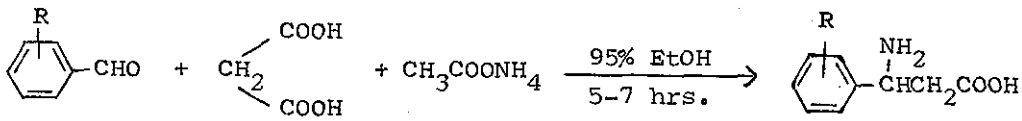
Table III shows each compound of the B class exhibits a lower P=O stretching band absorption (1210-1218 cm^{-1}) than the corresponding isomer of the A class (1228-1235 cm^{-1}); this contrast is very similar to that of 4-methylcyclophosphamides (slow B 1218 cm^{-1}, fast A 1231 cm^{-1}).[8] Thus, it is possible to assign the relative configuration of these 4-arylcyclophosphamide isomers based on the 4-methylcyclophosphamide isomers: the fast migrating A is cis with the spatial arrangement of 4-Ar(eq)-2-NR_2(ax) or 4-Ar(ax)-2-NR_2(eq), and the slow migrating B is trans with the spatial arrangement of 4-Ar(eq)-2-NR_2(eq). The cis-trans isomerism is defined with respect to the relative orientation of the 4-aryl substituent and the oxygen atom of the P=O bond.



cis trans

The proton nmr data in Table IV were consistent with the structures, especially when compared with the data for the parent, cyclophosphamide.[9] Thus, signals for C-5(2H), NR_2(8H), and C-6(2H) of these new 4-arylcyclophosphamides fell in the same ranges, respectively, as those for cyclophosphamide; the NH signals were identified by D_2O exchange experiments; and the signals for C-4(1H) moved downfield from that in cyclophosphamide owing to the 4-aryl substituents. The following characteristics were observed when cis and trans isomers were compared. Thus, C-5(2H) signal in cis A is downfield from that in trans B; NH signal in cis A is downfield(broad) from that in trans B(sharp); and the signal positions of NR_2(8H) and aryl protons are essentially unaffected by the cis-trans isomerism.

Table I. 3-Aryl-3-aminopropionic Acids

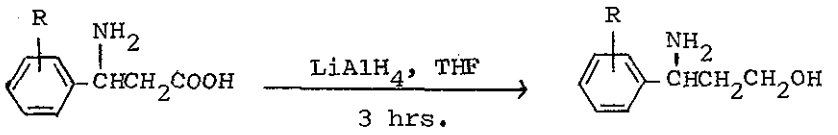


1-9

Compd.	R	mp(°C,obs.) mp(°C,lit.)	% Yield	Mass Spectra(M^+)
1	H	220.5-221 216(4)	52.5	165
2	2-CH_3	237-238 242(10)	32.1	179
3	3-CH_3	221-222 225(10)	63.2	179
4	4-CH_3	221-221.5 226(10)	96.2	179
5	3-OCH_3	213-214 216(11)	56.3	195
6	4-OCH_3	237-239 243(11)	92.2	195
7	2-Cl	246-247 245(12)	91.2	199,201
8[a]	3-Cl	242-243	90.3	199,201
9	4-Cl	242.5-243 245(12)	96.7	199,201

a. New compound.

Table II. 3-Aryl-3-*aminopropanols*



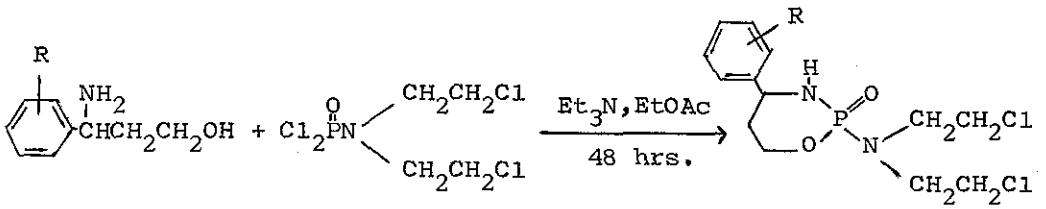
1-9 10-18

Compd.	R	mp(°C,obs.) mp(°C,lit.)	bp(°C/mm Hg,obs.) bp(°C/mm Hg,lit.)	% Yield	Mass Spectra(M^+)
10	H	71-72 73(13)	132-134/4	86.1	151
11	2-CH_3	46-47 b(14)	155/8	88.9	165
12[a]	3-CH_3	50-53.5	139.5/8	91.7	165
13[a]	4-CH_3	81-81.5		94.0	165
14	3-OCH_3	41-45(15)	167-169/8 105-115/0.05(15)	61.1	181
15	4-OCH_3	82-83 85(13)		96.9	181
16	2-Cl	65-67 b(14)		88.2	185,187
17	3-Cl	61-63 63-65(15)		73.7	185,187
18[a]	4-Cl	84.5-86.5		97.0	185,187

a. New compounds.

b. We have no access to the original article.

Table III. 4-Arylcyclophosphamides



10-18 19 20-28

Compd.[a]	R	mp (°C)	Mass Spectra(M^+)	cm^{-1} ir (ν P=O)[b]	% Yield[c]
20A	H	130.5-132	336,338	1230	33.5
20B	H	114-116	336,338	1212	28.0
21A	2-CH_3	128.5-130	350,352	1234	36.8
21B	2-CH_3	152-153	350,352	1214	31.7
22A	3-CH_3	84-86	350,352	1232	36.5
22B	3-CH_3	126-127.5	350,352	1210	32.1
23A	4-CH_3	106-107.5	350,352	1229	29.1
23B	4-CH_3	150.5-152	350,352	1212	28.2
24A	3-OCH_3	73.5-74.5	366,368	1228	48.6
24B	3-OCH_3	79-80.5	366,368	1211	43.2
25A	4-OCH_3	96.5-98	366,368	1234	35.0
25B	4-OCH_3	102-103.5	366,368	1216	21.6
26A	2-Cl	119-120.5	370,372	1232	23.8
26B	2-Cl	127-129	370,372	1217	17.7
27A	3-Cl	92-93.5	370,372	1235	29.8
27B	3-Cl	124-126	370,372	1218	17.5
28A	4-Cl	104-105.5	370,372	1230	34.0
28B	4-Cl	163-165	370,372	1212	48.5

a. All new compounds with satisfactory elementary analysis.

b. Recorded by a Perkin Elmer IR Model 297 Infrared Spectrophotometer using KBr tablets, carbon disulfide solutions, and mixtures with liquid paraffin. These compounds are practically insoluble in carbon tetrachloride.

c. Crude yields from chromatography.

Table IV. Proton nmr Spectra of 4-Arylcyclophosphamides[a]

Compd.	R	C-5(2H)	N-H[c]	NR_2-H(8H)	C-6(2H)	C-4(1H)	Aryl group Aromatic H	Aryl group R-H
20A	H	2.11(q)	3.08-3.17	3.35-3.75	4.15-4.45	4.50-4.66	7.25-7.53	
20B	H	1.81-1.95	2.82	3.42-3.65	4.04-4.44	4.52-4.72	7.28-7.35	
21A	2-CH_3	2.06(q)	2.88-3.02	3.40-3.73	4.16-4.47	4.71-4.96	7.10-7.86	2.34
21B	2-CH_3	1.77-1.94	2.63	3.45-3.66	4.07-4.60	4.85-4.99	7.11-7.52	2.34
22A	3-CH_3	2.10(q)	2.94-3.04	3.40-3.73	4.16-4.45	4.52-4.63	7.08-7.31	2.36
22B	3-CH_3	1.82-1.96	2.79	3.47-3.65	4.04-4.44	4.52-4.70	7.06-7.28	2.36
23A	4-CH_3	2.08(q)	2.98-3.10	3.33-3.72	4.14-4.40	4.44-4.58	7.13-7.42	2.33
23B	4-CH_3	1.81-1.96	2.78	3.45-3.71	4.04-4.47	4.54-4.71	7.07-7.28	2.34
24A	3-OCH_3	2.13(q)	2.91-3.02	3.41-3.67	4.15-4.49	4.51-4.74	6.80-7.38	3.83
24B	3-OCH_3	1.83-1.99	2.74	3.47-3.73	4.05-4.48	4.57-4.73	6.78-7.60	3.82
25A	4-OCH_3	2.08(q)	2.91-3.03	3.40-3.73	4.14-4.42	4.45-4.68	6.86-7.46	3.80
25B	4-OCH_3	1.81-1.95	2.72	3.46-3.65	4.03-4.47	4.52-4.70	6.85-7.31	3.80
26A	2-Cl	2.08(q)	2.83-2.99	3.40-3.72	4.06-4.48	4.92-5.24	7.27-8.15	
26B	2-Cl	1.72-1.90	2.83	3.49-3.67	4.06-4.62	5.05-5.26	7.21-7.68	
27A	3-Cl	2.09(q)	3.02-3.16	3.40-4.73	4.15-4.43	4.47-4.76	7.27-7.58	
27B	3-Cl	1.81-1.94	2.98	3.42-3.72	4.05-4.47	4.55-4.73	7.28-7.34	
28A	4-Cl	2.09(q)	3.05-3.17	3.31-3.68	4.16-4.43	4.47-4.77	7.28-7.53	
28B	4-Cl	1.82-1.93	2.77	3.47-3.71	4.07-4.49	4.55-4.73	7.28-7.33	
Cyclophosphamide[b]		1.85-1.95	variable	3.3-3.65	4.2-4.5	3.1-3.3		

a. Recorded on a JEOL FX-100 High Resolution NMR Instrument using $CDCl_3$ as solvent. The chemical shifts are reported in *ppm downfield* from internal TMS.

b. Ref. 9.

c. Identified by D_2O exchange experiment: broad in A and sharp in B.

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