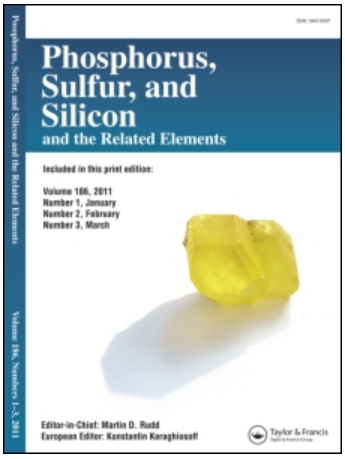

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SYNTHESIS AND ANTICANCER SCREENING OF DIASTEREOISOMERIC 4,5-DIPHENYL- AND 3-METHYL-4,5-DIPHENYLCYCLOPHOSPHAMIDES

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Communication

SYNTHESIS AND ANTICANCER SCREENING OF DIASTEREOISOMERIC 4,5-DIPHENYL- AND 3-METHYL-4,5-DIPHENYLCYCLOPHOSPHAMIDES

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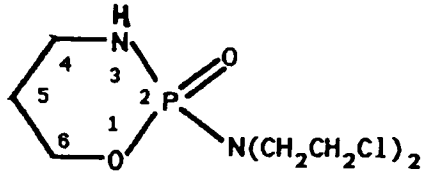
The four possible diastereoisomers of 4,5-diphenylcyclophosphamides (**2–5**) and their N-methyl analogues (**6–9**) have been synthesized via condensation of aminopropanols **10** and **11** (threo- and erythro) with bis-(2-chloroethyl)-phosphoramidic dichloride **12**. Anticancer screening tests against L 1210 lymphoid leukaemia in mice did not show any therapeutic activity.

Key words: Diastereoisomeric 4,5-diphenylcyclophosphamides; anticancer screening.

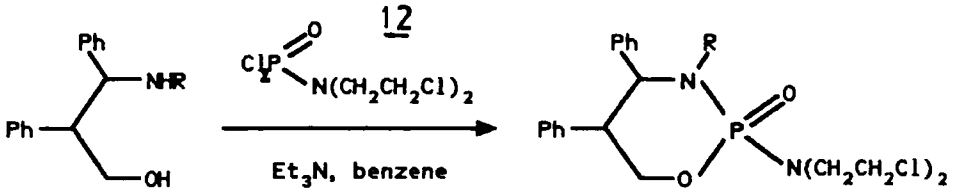
Racemic cyclophosphamide, **1**, is one of the most widely used chemotherapeutic agents in the treatment of many types of cancer. During the last years much effort has been made to develop strategically substituted analogues of **1** with improved activity.[1]



cyclophosphamide, 1

A series of diastereoisomeric 4-arylcyclophosphamides,[2,3] 5-phenyl-[4] and 6-phenylcyclophosphamides[5] have been synthesized. Significant difference in anticancer activity against L 1210 lymphoid leukaemia in mice has been found for the cis- and trans-4-phenylcyclophosphamide.[3]

It is our aim to extend the synthesis and structure studies to diastereoisomeric 4,5-diphenylcyclophosphamides **2–5** and their N-methyl analogues **6–9**. Disubstitution at C-4,5 generates a second and third chiral center in addition to P-2 resulting in four diastereoisomeric racemates in every case. The relative configurations and the favoured conformations of these compounds were published previously by some



threo or erythro 10 R = H 2 - 5

threo or erythro 11 R = CH_3 6 - 9

SCHEME

of us.[6] The starting diastereoisomeric 3-amino-(**10**) and 3-methylamino-(**11**)-2,3-diphenylpropanols were prepared in two steps from methylphenylacetate and hydrobenzamide[7,8] or benzylidenemethylamine.[9]

The four aminoalcohols (comps. **10** and **11**, threo- and erythro-) were allowed to react at room temperature with equimolar amount of bis-(2-chloroethyl)-phosphoramidic dichloride **12** in the presence of 2 equiv. of triethylamine in benzene.

The crude products were chromatographed on silica gel to give two isomers in nearly equal amounts in each case. Compounds **2** and **3** were separated by fractional crystallization (see Table 1).

ANTICANCER SCREENING DATA

The in vivo anticancer activity of the newly synthesized diastereoisomeric 4,5-diphenylcyclophosphamides was evaluated against L 1210 lymphoid leukaemia in B6D2F1 mice. As a positive control served cyclophosphamide **1**. Antitumour activity was evaluated determining the mean survival time of treated groups compared to control mice and was expressed as a percentage (% T/C).

Diastereoisomeric 4,5-diphenylcyclophosphamides **2–9** did not affect the survival time in doses 1 × 200, 1 × 400 and 5 × 65 mg/kg. All of 1 × 200 mg/kg

TABLE I

Synthesis of diastereoisomeric 4,5-diphenylcyclophosphamides **2–9**

Comp.[a]	R	Start. comp.	React. time (h)	m.p. °C[b]	R_f[c]	% Yield[d]
2	H	threo-*10*	6	108–109	0.38	7[e]
3	H	threo-*10*	6	145–150	0.38	39[e]
4	H	erythro-*10*	72	122–124	0.56	28
5	H	erythro-*10*	72	125–126	0.31	31
6	CH_3	threo-*11*	24	126–128	0.57	50
7	CH_3	threo-*11*	24	115–116	0.42	42
8	CH_3	erythro-*11*	72	129–130	0.61	48
9	CH_3	erythro-*11*	72	135–137	0.32	39

[a]For all new compounds the mass spectra correspond to the molecular formula; [b]after recrystallization from 1-Pr_2O; [c]ether:hexane:MeOH = 40:9:1, silica gel; [d]crude yield from chromatography; [e]yield of pure product separated by fractional crystallization.

cyclophosphamide treated mice were "cured" (alive more than 1 month). Cyclophosphamide at 1 × 65 mg/kg resulted in 189% T/C whereas 1 × 400 mg/kg dose was toxic.

EXPERIMENTAL

Threo- and erythro-3-aminopropanols **10** were prepared according to References 7 and 8, threo- and erythro-3-methylaminopropanols **11**, according to Reference 9.

2-[Bis(2-chloroethyl)amino]-4,5-diphenyl-2H-1,3,2-oxazaphosphorinane-2-oxide (4,5-diphenylcyclophosphamides) **2–9**. To 5 mmole of **10** or **11** (threo- or erythro-) and 5 mmol of **12**[10] in 20 ml of dry benzene, 12 mmol of Et_3N was added under stirring at room temperature for some hours (Table I). The triethylamine hydrochloride precipitate was discarded and the solvent removed from the filtrate in vacuo to give the crude product as a pale yellow oil.

The crude product from threo-**10** after trituation with dry ether and evaporation was crystallized from benzene-diisopropylether to give the higher melting isomer **3**. Combined filtrates of **3** after concentration, trituation with ether-pentane, evaporation and crystallization from diisopropylether gave the lower melting isomer **2**.

Column chromatography of the crude products from erythro-**10**, threo- and erythro-**11** (70–230 mesh silica gel, eluting successively with ether:petroleum ether 1:1; ether:petroleum ether: MeOH 10:1:0.5; ether:MeOH 40:1) led to isolation of fractions, containing slower eluting isomers **5**, **7**, **9** and faster eluting isomers **4**, **6**, **8**.

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