SYNTHESIS OF UNSYMMETRICAL NN'-DIAMIDOPHOSPHORYL DERIVATIVES OF AMINOCYCLOHEXANE AND STEREOISOMERIC 4-AMINOCYCLOHEXANE-CARBOXYLIC ACID

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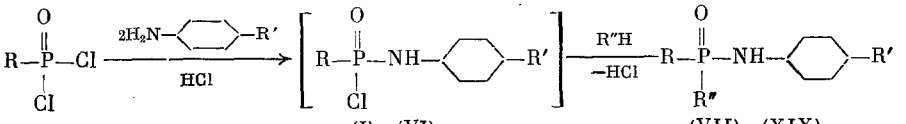
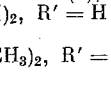
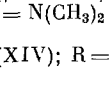
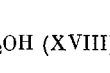
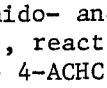
Symmetrical triamides of phosphoric and thiophosphoric acids, $R'N{-}P(X)(NR)_2$ (X = O or S), containing two identical substituents NR at the phosphorus, comprise an extensively-studied group of phosphorus–nitrogen compounds, noteworthy among which are derivatives of aminocyclohexane and aminocyclohexylalkanoic acids, which display antitumor, antileukemia, and chemosterilant activity [1-3]. There have been virtually no studies on the methods of preparation, properties, and uses of unsymmetrical triamides in which the phosphorus is attached to three different amide residues. The introduction of one, two, or three amide groups of differing basicity has considerable effects on the electron density at the heteroatoms, resulting in changes in the reactivity of the molecules, and could also give rise to great diversity and selectivity of biological effects.

We here describe the synthesis and structures of some novel unsymmetrical triamides of phosphoric acid containing cytotoxic ethyleneimino or di(2-chloroethyl)amino groups, aminocyclohexane residues, ethyl cis- or trans-4-aminocyclohexylcarboxylate (4-ACHC) residues, or other amines.

Compounds (VII)-(XIX) were synthesized by phosphorylating the amines with amidophosphoryl chlorides in the presence of the reactant amine or Et_3N as HCl acceptors:



(I)–(VI) (VII)–(XIX)

$R = N(CH_3)_2$, $R' = H$ (I); $R = N(CH_3)_2$, $R' =$ cis- and trans- $COOC_2H_5$ (II) and (III); $R = N(CH_2CH_2Cl)_2$, $R' = H$ (IV); $R = N(CH_2CH_2Cl)_2$, $R' =$ cis- and trans-$COOC_2H_5$ (V) and (VI); $R = N(CH_3)_2$, $R' = H$, $R'' =$  (VII); $R = N(CH_3)_2$, $R' = H$, $R'' =$  (VIII); $R = N(CH_3)_2$, $R' =$ cis- and trans-$COOC_2H_5$, $R'' =$  (IX) and (X); $R = N(CH_2CH_2Cl)_2$, $R' = H$, $R = N(CH_3)_2$ (XI); $R = N(CH_2CH_2Cl)_2$, cis- and trans-$R' = COOC_2H_5$, $R'' = N(CH_3)_2$ (XII) and (XIII); $R = N(CH_2CH_2Cl)_2$, $R' =$ trans-$COOC_2H_5$, $R'' =$  (XIV); $R = N(CH_2CH_2Cl)_2$, $R' = H$, $R'' =$  (XV); $R = N(CH_2CH_2Cl)_2$, $R' =$ cis- and trans-$COOC_2H_5$, $R'' =$  (XVI) and (XVII); $R = N(CH_2CH_2Cl)_2$, $R' = H$, $R'' = NHCH_2CH_2OH$ (XVIII); $R = N(CH_3)_2$, $R' =$ cis-$COOC_2H_5$, $R'' =$  (XIX).

The starting materials comprised NN-dimethylamido- and NN-di(2-chloroethyl)amidophosphoryl dichlorides ($R = N(CH_3)_2$, $N(CH_2CH_2Cl)_2$), reaction of which with a twofold excess of aminocyclohexane or ethyl cis- and trans- 4-ACHC gave the NN'diamidophosphoryl monochlorides (I)-(VI). The formation of (I)-(VI) was confirmed by their PMR spectra, but in view of their instability they were not isolated from the reaction mixtures, but after separation of the hydrochlorides they were reacted immediately with the third amine. Both steps were carried out in dry solvents (ether or benzene) at −5 to 0°C. Under

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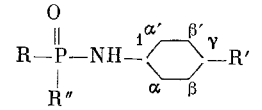
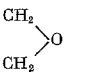
TABLE 1. Unsymmetrical Triamides of Phosphoric Acid (VII)-(XIX)

Compound	Yield, %	Mp, °C (from ether)	Found/Calculated, %				Empirical formula
			C	H	Cl	P	
NN-Dimethyl-N'-cyclohexyl-N"-ethylenephosphorotriamide (VII	50	80–82	52,0 51,9	9,3 9,6	–	13,0 13,4	$C_{10}H_{22}N_3OP$
NN-Dimethyl-N'-3-oxapentamethylene-N"-cyclohexyl-phosphorotriamide (VIII)	35	92–94	52,6 52,4	9,6 9,5		10,9 11,2	$C_{12}H_{26}N_3O_2P$
Ethyl N-(N'N'-dimethylamido-N"-morpholido)phosphoryl-cis-4-aminocyclohexanecarboxylate (IX)	30	69–70	52,4 52,2	8,3 8,2		9,0 9,0	$C_{15}H_{30}N_3O_4P$
Ethyl N-(N'N'-dimethylamido-N"-morpholido)phosphoryl-trans-4-aminocyclohexanecarboxylate (X)	27	75–76	52,1 52,2	8,4 8,2		8,8 9,0	$C_{15}H_{30}N_3O_4P$
NN-Dimethyl-N'N'-di-(2-chloroethyl)-N"-cyclohexyl-phosphorotriamide (XI)	51	86–88	43,8 43,6	8,0 7,9	20,9 21,5	9,1 9,4	$C_{12}H_{26}Cl_2N_3OP$
Ethyl N-[N'N'-dimethylamido-N"N"-di-(2-chloroethyl)-amido]-phosphoryl-cis-4-aminocyclohexanecarboxylate (XII)	35	68–71	44,9 44,8	7,5 7,5	17,3 17,6	7,3 7,7	$C_{15}H_{30}Cl_2N_3O_3P$
Ethyl N-[N'N'-dimethylamido-N"N"-di-(2-chloroethyl)-amido]-phosphoryl-trans-4-aminocyclohexanecarboxylate (XIII)	22	91–94	44,6 44,8	7,5 7,5	17,2 17,6	7,6 7,7	$C_{15}H_{30}Cl_2N_3O_3P$
Ethyl N-[N'N'-di-(2-chloroethyl)amido-N"-morpholido]-phosphoryl-trans-4-aminocyclohexanecarboxylate (XIV)	40	109–110	46,0 46,0	7,4 7,3	16,2 16,0	7,2 7,0	$C_{17}H_{32}Cl_2N_3O_4P$
NN-Di-(2-chloroethyl)-N'-cyclohexyl-N"-ethylene-phosphorotriamide (XV)	43	54–56	43,6 43,9	7,5 7,4	21,6 21,6	9,3 9,4	$C_{12}H_{24}Cl_2N_3OP$
Ethyl N-[N'N'-di-(2-chloroethyl)amido-N"-ethylenimido]-phosphoryl-cis-4-aminocyclohexanecarboxylate (XVI).	44	53–54	45,3 45,0	7,1 7,1	17,4 17,7	7,2 7,7	$C_{15}H_{28}Cl_2N_3O_3P$
Ethyl N-[N'N'-di-(2-chloroethyl)amido-N"-ethylenimido]-phosphoryl-trans-4-aminocyclohexanecarboxylate (XVII)	29	97–100	45,1 45,0	7,2 7,1	17,5 17,7	7,6 7,7	$C_{15}H_{28}Cl_2N_3O_3P$
NN-Di-(2-chloroethyl)-N'-2-hydroxyethyl-N"-cyclohexyl-phosphorotriamide (XVIII)	52	101–102 ($CHCl_3$–ether)	41,4 41,6	7,3 7,5	20,5 20,5	8,9 8,9	$C_{12}H_{26}Cl_2N_3O_2P$
Ethyl N-(N'N'-dimethylamido-N"-cyclohexylamido)-phosphoryl-cis-4-aminocyclohexanecarboxylate (XIX)	15	104–106	56,8 56,8	9,6 9,5		9,0 8,6	$C_{17}H_{34}N_3O_3P$

TABLE 2. Chemical Shifts (ppm) of Carbon Atoms in the ^{13}C NMR Spectra of Unsymmetrical Triamides (VII)-(XIV) and (XVI)-(XIX)



Compound	NCH_3	NCH_2	CH_2Cl	OCH_2	CH_3	C′
(VII) *	36,71d					49,56
(VIII)	36,94 d					49,71
(IX)	36,94d			60,10	14,01	47,42
(X)	37,10d			60,42	14,19	49,56
(XI)	36,87d	48,85d	42,55d			49,70
(XII)	36,94d	48,84d	42,52	60,02	14,05	47,44
(XIII)	37,21d	49,21d	42,91d	60,28	14,23	49,82
(XIV)		48,93	42,80d	60,32	14,23	49,90
(XVI) *		49,65 d	42,69	60,10	14,08	47,29
(XVII) *		49,84 d	42,83d	60,32	14,23	49,60
(XVIII) †		49,33 d	42,73			50,05
(XIX)	36,97d			60,09	14,08	47,21
						49,83

Compound	C_α	C_β	C_γ	C=O		
(VII) *	35,97d.d	24,92	25,29			
(VIII)	36,35 d.d	24,99	25,29		44,86	67,26 d
(IX)	32,06 d.d	24,86	39,96	174,92	44,88	67,13 d
(X)	35,41 d.d	28,24	42,50	175,46	45,08	67,40d
(XI)	35,71 d.d	24,84	25,21			
(XII)	32,01 d.d	24,84	39,97	174,94		
(XIII)	35,33 d.d	28,20	42,54	175,53		
(XIV)	35,37 d.d	28,16	42,39	175,39	45,19	67,28 d
(XVI) *	31,99 d.d	24,76	39,97	174,90		
(XVII) *	35,29 d.d	28,16	42,43	175,46		
(XVIII) †	36,04 d.d	24,95	25,25			
(XIX)	32,14 d	24,80	40,00	174,80		
	36,29 d	25,06	25,33	174		

*Chemical shifts of the C atoms of the ethylenimine ring: 22.81 d (VII), 23.64 d (XVI), 23.87 d (XVII).
†Chemical shift of C in CH_2OH, 63.21 d.

these conditions, replacement of the third chlorine required a much longer reaction time (35-40 h) as a result both of its reduced reactivity and of steric hindrance. The triamides thus obtained (VII)-(XIX) were difficult to crystallize compounds, the yields ranging from 20 to 65%. The constants and elemental analyses of (VII)-(XIX) are given in Table 1.

It is noteworthy that at higher temperatures, and depending on the order of addition of the reactant amines, in addition to the required products (VII)-(XIX), there may also be formed small amounts (up to 10-15%) of symmetrical triamides with two identical amide groups, as shown by the PMR spectra of the reaction mixtures. The compounds were isolated by fractional crystallization. The course of the reactions was followed and the completion of the reaction established by TLC on alumina, and by the amounts of the hydrochlorides of the appropriate amines isolated. The structures of the products were confirmed by their PMR and ^{13}C NMR spectra. In all the compounds, the signals for the cyclohexane ring protons in the PMR spectra were seen as a broad multiplet centered at ~1.47 ppm. The signals for the protons of the $(CH_3)_2N$ group in (I)-(III), (VII)-(XIII), and (XIX), and the ethylenimine ring in (VII) and (XV)-(XVII) were seen as doublets at 2.60-2.62 and 1.93-1.98 ppm respectively, and those for $(ClCH_2CH_2)_2N$ in (IV)-(VI) and (XI)-(XVIII) as a broad multiplet (3.07-3.73 ppm), overlapping in (XIV) with the multiplet for the morpholine protons. The characteristic signals for the ester grouping in (II), (III), (V), (VI), (IX), (X), (XII)-(XIV), (XVI), (XVII), and (XIX) were present at 1.02-1.14 ppm (t, 3H, OCH_2CH_3) and 3.98-4.04 ppm (q, 2H, OCH_2).

The chemical shifts of the C atoms in the ^{13}C NMR spectra are given in Table 2. These spectra show that the peaks for the carbons two or three bonds removed from the phosphorus are split into doublets, the $^{2}J_{PNC}$ values being considerably less than $^{3}J_{PNCC}$. The α-atoms of the cyclohexane ring are nonequivalent. The diastereotopicity of these atoms is due to the asymmetrical substitution at the phosphorus [4], and the difference in the chemical shifts of the α- and α'-atoms is dependent on the nature of the two other substituents.

Experimental

The PMR spectra of the pure compounds and the reaction mixtures were obtained on a Perkin-Elmer R-22 spectrometer (90 MHz) in $CDCl_3$ relative to HMDS. ^{13}C NMR spectra were obtained on a Tesla BS-567 A spectrometer (25.14 MHz) with complete suppression of coupling with the protons in $CDCl_3$ relative to TMS.

NN-Dimethylamidophosphoryl dichloride was obtained as described in [5], NN-di-(2-chloroethyl)amidophosphoryl dichloride as in [6], and ethyl cis- and trans-4-ACHC as in [7]. All the reactions and the purification of the products were carried out in dry solvents.

General Method of Preparation of Phosphorotriamides (VII)-(XIX). To a solution of 0.025 mole of the NN-dimethyl- or NN-di-(2-chloroethyl)-amidophosphoryl dichloride in 200 ml of dry ether or benzene was added slowly, dropwise with cooling at −5 to 0°C 0.05 mole of aminocyclohexane or ethyl cis- (or trans)-4-ACHC in 100 ml of dry ether. The mixture was stirred for 1 h at 0°C and 2 h at ~20°C, and kept for 10-12 h. The hydrochloride which separated (theoretical amount) was filtered off. The solution of the monochloride (I)-(VI) was cooled to −5 to 0°C, and treated with stirring with 0.05 mole of morpholine, 0.05 mole of ethanolamine, 0.05 mole of cyclohexylamine, or 0.025 mole of ethylenimine and 0.025 mole of Et_3N or saturated Me_2NH. When the reaction was complete (as shown by TLC on alumina, eluent benzene–methanol–ether, 4:1:2), the amine hydrochloride which had separated was filtered off, the filtrate evaporated under reduced pressure, and the residue recrystallized to give (VII)-(XIX) (Table 1).

Conclusions

Phosphorylation of some amines with amidophosphoryl chlorides has given the unsymmetrical NN'-diamidophosphoryl derivatives of aminocyclohexane and the stereoisomeric 4-aminocyclohexanecarboxylic acid, and their ^{13}C NMR spectra have been examined.

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