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DERIVATIVES OF CYCLOHEXYLAMINE AND SOME AROMATIC AMINES CONTAINING THE N-TETRAMETHYLDIAMIDO(THIO)PHOSPHORYL GROUP

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N-Tetramethyldiamidophosphoryl (TMDAP) derivatives of aminocyclohexanecarboxylic acids have considerable antitumor activity relative to specific transplantable tumors [1, 2]. In order to study the relationship between the antitumor and chemical sterilizing activity and the structure of compounds containing the cytoactive TMDAP group, we synthesized N-TMDAP-cis-4-aminocyclohexylacetic acid, N-TMDAP-p-aminophenylacetic acid, N-TMDAP-p-amino-N-acetyl-DL-phenylalanine, their ethylenimides, N-[tetramethyldiamido(thio)phosphoryl]aniline, N-[tetramethyldiamido(thio)phosphoryl]cyclohexylamine, and N-[tetramethyldiamido(thio)phosphoryl]morpholine.

The benzyl esters of cis-4-aminocyclohexylacetic acid and p-amino-N-acetyl-DL-phenylalanine served as starting materials. The condensation of these esters with the acid chloride of N-tetramethyldiamidophosphoric acid [3, 4] in the presence of triethylamine gave the benzyl esters of N-TMDAP-cis-4-aminocyclohexylacetic acid (I) and N-TMDAP-p-amino-N-acetyl-DL-phenylalanine (II). Catalytic hydrogenolysis of (I) and (II) gives N-TMDAP-cis-4-aminocyclohexylacetic acid (III) and N-TMDAP-p-amino-N-acetyl-DL-phenylalanine (IV). The Schotten–Baumann condensation of p-aminophenylacetic acid with the acid chloride of N-tetramethyldiamidophosphoric acid yielded N-TMDAP-p-aminophenylacetic acid (V). The reaction of (IV) and (V) with ethylenimine in the presence of 1,3-dicyclohexylcarbodiimide gave the ethylenimides of N-TMDAP-p-amino-N-acetyl-DL-phenylalanine (VI) and N-TMDAP-p-aminophenylacetic acid (VII).

$PSCl_3$ was used in the synthesis of N-tetramethyldiamido(thio)phosphoryl derivatives of cyclic amines. The reaction of $PSCl_3$ with the hydrochloride salts of aniline, cyclohexylamine, and morpholine yielded N-[dichloro(thio)phosphoryl]aniline (VIII), N-[dichloro(thio)phosphoryl]cyclohexylamine (IX), and N-[dichloro(thio)phosphoryl]morpholine (X). The condensation of these compounds with excess dimethylamine gave N-[tetramethyldiamido(thio)phosphoryl]aniline (XI), N-[tetramethyldiamido(thio)phosphoryl]cyclohexylamine (XII), and N-[tetramethyldiamido(thio)phosphoryl]morpholine (XIII). The properties of (I)-(XIII) are given in Table 1.

EXPERIMENTAL

Benzyl Ester of N-(Tetramethyldiamidophosphoryl)-cis-4-aminocyclohexylacetic Acid (I). A sample of 1.56 g (0.009 mole) acid chloride of N-tetramethyldiamidophosphoric acid in 5 ml abs. benzene and 0.91 g (0.009 mole) triethylamine in 3 ml abs. benzene were added to 2.28 g (0.009 mole) benzyl ester of cis-4-aminocyclohexylacetic acid in 10 ml abs. benzene. The mixture was heated at 100°C for 8 h and left overnight in a refrigerator. The precipitate was filtered off. The filtrate was washed with water and dried over $MgSO_4$. The solvent was removed in vacuum. The oily precipitate was triturated in petroleum ether and dried in a vacuum dessicator to yield 1.92 g (I).

Benzyl ester (II) was prepared in the same way.

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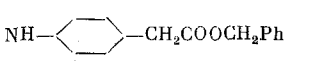
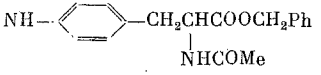
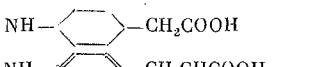
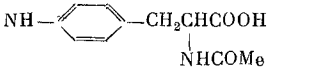
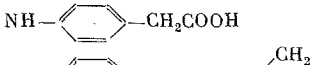
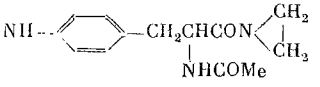
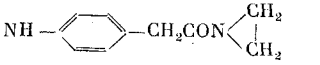
TABLE 1. Properties of N-[Tetramethyldiamido(thio)phosphoryl]amide Derivatives $R_2P(X)-R'$

Compound	R	X	R'	Recrystallization solvent	Mp, °C	Yield, %	Found, %		Chemical formula	Calculated, %	
							N	Cl		N	Cl
(I)	$(CH_3)_2N$	O		Benzene–petr. ether	49–54*	57	11,04; 11,14	–	$C_{19}H_{32}N_3O_3P$	11,01	–
(II)	Same	O		–	Oil	61	12,86; 12,02	–	$C_{22}H_{31}N_4O_4P$	12,54	–
(III)	"	O		Acetone	128–131	53	14,38; 14,54	–	$C_{12}H_{25}N_3O_3P$	14,42	–
(IV)	"	O		Chloroform–petr. ether	37–40	64	15,82; 15,68	–	$C_{15}H_{25}N_4O_4P$	15,72	–
(V)	"	O		Ethanol	188–191	63	14,59; 14,91	–	$C_{12}H_{20}N_3O_3P$	14,73	–
(VI)	"	O		Ethyl acetate–petr. ether	35–38	33	18,52; 18,03	–	$C_{17}H_{28}N_5O_3P$	18,36	–
(VII)	Me_2N	O		Benzene–ether	42–48*	56	7,56; 7,59	–	$C_{14}H_{23}N_4O_2P$	7,47	–
(VIII)	Cl	S		Chloroform–petr. ether	181–183	50	6,19; 5,90	31,05; 31,00	$C_6H_6NPSCl_2$	6,19	31,37
(IX)	Cl	S		–	Oil	98	5,70; 5,68	31,00; 31,71	$C_6H_{12}NPSCl_2$	6,03	30,55
(X)	Cl	S		Benzene–petr. ether	29–31	79	6,41; 7,07	32,41; 32,58	$C_4H_8NOPSCl_2$	6,36	32,22
(XI)	Me_2N	S		Ethanol	186–188	51	17,32; 17,18	–	$C_{10}H_{18}N_3PS$	17,27	–
(XII)	Same	S		–	Oil	70	16,61; 16,92	–	$C_{10}H_{24}N_3PS$	16,85	–
(XIII)	"	S		–	Oil	62	17,49; 17,88	–	$C_8H_{20}N_3OPS$	17,70	–

* Melts with decomposition.

N-(Tetramethyldiamidophosphoryl)-cis-4-aminocyclohexylacetic Acid (III). A sample of 2.2 g (I) in 50 ml ethanol was hydrogenated over palladium black until no further hydrogen was taken up. The catalyst was filtered off and the solvent was evaporated in vacuum. The residue was triturated in petroleum ether to yield 0.9 g (III).

A sample of N-(tetramethyldiamidophosphoryl)-p-amino-N-acetyl-DL-phenylalanine (IV) was obtained analogously.

N-(Tetramethylamidophosphoryl)-p-aminophenylacetic Acid (V). A sample of 1.14 g (0.007 mole) p-aminophenylacetic acid and 0.8 g Na_2CO_3 in 10 ml distilled water was cooled to 10°C and then 1.34 g (0.007 mole) acid chloride of N-tetramethyldiamidophosphoric acid in a solution of 2.4 g Na_2CO_3 and 40 ml distilled water was added with stirring over 30 min. The mixture was cooled, left overnight at ~ 20°C, and filtered. The filtrate was neutralized with dilute HCl to pH 4. The precipitate was filtered off, recrystallized, and dried in a vacuum dessicator to yield 1.2 g (V).

Ethylenimide of N-(Tetramethyldiamidophosphoryl)-p-aminophenylacetic Acid (VII). A sample of 0.25 g (0.0012 mole) 1,3-dicyclohexylcarbodiimide in 4 ml DMF and 0.05 g (0.0012 mole) ethylenimine in 4 ml DMF was added to 0.36 g (0.0012 mole) (V) in 4 ml DMF. The mixture was cooled and left overnight at ~20°C. The precipitate was filtered off and the filtrate was evaporated in vacuum. The residue was triturated in abs. ether, filtered off, recrystallized, and dried in a vacuum dessicator to yield 0.19 g (VII).

Ethylenimide (VI) was prepared analogously.

N-[Dichloro(thio)phosphoryl]aniline (VIII). A sample of 20 ml (1.00 mole) $PSCl_3$ was added to 3.23 g (0.025 mole) hydrochloride salt of aniline and heated at reflux for 24 h until the salt was completely dissolved. Excess $PSCl_3$ was distilled off in vacuum and the residue was triturated in ether to yield 3.5 g (VIII).

Samples of N-[dichloro(thio)phosphoryl]cyclohexylamine (IX) and N-[dichloro(thio)phosphoryl]morpholine (X) were prepared analogously.

N-[Tetramethyldiamido(thio)phosphoryl]aniline (XI). A sample of 4.20 g (0.04 mole) dimethylamine in benzene was added to 2.25 g (0.01 mole) (VIII) in 30 ml benzene with stirring and cooling. The mixture was left overnight at ~ 20°C. The hydrochloride salt of dimethylamine was filtered off and the filtrate was heated for 8 h at 100°C. The benzene layer was separated, washed with water, and dried over $MgSO_4$. The solvent was distilled off in vacuum and the residue was triturated with ether and recrystallized to yield 1.2 g (XI).

Samples of N-[tetramethyldiamido(thio)phosphoryl]cyclohexylamine (XII) and N-[tetramethyldiamido(thio)-phosphoryl]morpholine (XIII) were prepared analogously.

CONCLUSIONS

1. N-(tetramethyldiamidophosphoryl)-cis-4-aminocyclohexylacetic acid, N-(tetramethyldiamidophosphoryl)-p-aminophenylacetic acid, N-(tetramethyldiamidophosphoryl)-p-amino-N-acetyl-DL-phenylalanine and their ethylenimides were synthesized.

2. The condensation of N-dichloro(thio)phosphoryl derivatives of cyclic amines with dimethylamine gave N-[tetramethyldiamido(thio)phosphoryl]aniline, N-[tetramethyldiamido(thio)phosphoryl]cyclohexylamine, and N-[tetramethyldiamido(thio)phosphoryl]morpholine.

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