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SYNTHESIS OF ALKYL ESTERS OF N,N-BIS(2-CHLOROETHYL)CARBAMOYL-α-AMINO ACIDS

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Currently one of the most promising directions in the chemotherapy of malignant tumors is the synthesis and study of cytotoxic derivatives of amino acids and peptides [1]. A study of urea derivatives also evokes considerable interest in recent years in view of their high biological and, in particular, antitumor activity [2, 3]. Although quite a large number of bis(2-chloroethyl)urea derivatives has been synthesized at the present time [4-7], still compounds of this type, containing α-amino acid and peptide moieties, have received little study up to now.

In view of this we undertook the synthesis of some alkyl esters of N,N-bis(2-chloroethyl)carbamoyl-α-amino acids, which have interest as potential cancerostatic agents. A method for the preparation of the indicated compounds, based on the reaction of bis(2-chloroethyl)amine with the alkyl esters of N-carbonyl-α-amino acids, is described in the literature [8], but it failed to find wide application due to the difficult availability of the starting optically active alkyl esters of N-carbonyl-α-amino acids [9] and the instability of the free bis(2-chloroethyl)amine [10]. Consequently, to obtain the alkyl esters of N,N-bis(2-chloroethyl)carbamoyl α-amino acids we employed the reaction of bis(2-chloroethyl)carbamoyl chloride with the alkyl esters of α-amino acids in the presence of triethylamine as the HCl acceptor [11].

$$(ClCH_2CH_2)_2NCOCl + H_2N-\underset{\displaystyle R}{\underset{|}{CH}}-COOR' \xrightarrow{Et_3N} (ClCH_2CH_2)_2N-\overset{\displaystyle O}{\overset{\|}{C}}-NH-\underset{\displaystyle R}{\underset{|}{CH}}-COOR'$$

(I)—(XIV)

The merits of this method consist in the use of readily available and quite stable starting compounds and in the high yields of the desired compounds (Table 1). The obtained compounds are viscous oils that are soluble in ether and insoluble in water; their homogeneity was established via TLC on Woelm neutral Al_2O_3. The chemical structure was confirmed by the elemental analysis results and IR spectroscopy.

EXPERIMENTAL

The IR spectra were taken on an IRS-22 spectrophotometer. The optical activity was measured in dioxane on a Gouan polarimeter. The starting bis(2-chloroethyl)carbamoyl chloride was obtained by reacting bis(2-chloroethyl)amine with phosgene and was purified by distillation [12]. The alkyl esters of the α-amino acids were isolated from the corresponding hydrochlorides in the customary manner [13].

General Procedure. To a stirred mixture of 1 mole of the alkyl ester of the α-amino acid and 1 mole of triethylamine in abs. ether at 0°C was added a solution of 1 mole of bis(2-chloroethyl)carbamoyl chloride in abs. ether. The stirred reaction mass was brought up to ~20°. The end of reaction was judged by the TLC results. The triethylamine hydrochloride precipitate was filtered, and the filtrate was evaporated.

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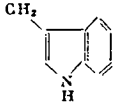
TABLE 1. $(ClCH_2CH_2)_2N-\underset{\underset{O}{\|}}{C}-NH-\underset{\underset{R}{|}}{CH}-COOR'$

Compounds	R	R'	Name	Yield, %	$[\alpha]_D^{20}$ (C=1)	R_f^*	Found, %			Empirical formula	Calculated, %		
							C	H	N		C	H	N
(I)	CH_3	CH_3	L-Ala	98,5	+3,70	0,57 A	40,48	6,02	9,98	$C_9H_{16}Cl_2N_2O_3$	39,86	5,94	10,33
(II)	C_4H_9	CH_3	L-Leu	95,0	−2,93	0,43 B	45,80	7,26	8,88	$C_{12}H_{22}Cl_2N_2O_3$	46,11	7,08	8,94
(III)	$(CH_2)_2SCH_3$	CH_3	L-Met	95,0	−3,90	0,62 A	40,09	6,12	8,45	$C_{11}H_{20}Cl_2N_2O_3S$	39,88	6,09	8,46
(IV)	H	C_2H_5	Gly	98,5	–	0,80 B	39,64	6,12	9,80	$C_9H_{16}Cl_2N_2O_3$	39,86	5,94	10,33
(V)	CH_3	C_2H_5	L-Ala	95,1	–	0,21 C	41,80	6,48	9,58	$C_{10}H_{18}Cl_2N_2O_3$	42,12	6,36	9,83
(VI)	C_3H_7	C_2H_5	L-Val	98,0	−21,0	0,75 B	46,29	7,28	8,92	$C_{12}H_{22}Cl_2N_2O_3$	46,01	7,08	8,94
(VII)	C_4H_9	C_2H_5	L-Ileu	98,4	−7,0	0,70 B	47,31	7,50	9,11	$C_{13}H_{24}Cl_2N_2O_3$	47,71	7,39	8,56
(VIII)	$CH_2C_6H_5$	C_2H_5	L-Phe	99,0	−24,9	0,70 B	53,28	6,23	7,97	$C_{16}H_{22}Cl_2N_2O_3$	53,19	6,14	7,75
(IX)		CH_3	L-Trp	97,8	–	0,57 A	52,84	5,50	10,85	$C_{17}H_{21}Cl_2N_3O_3$	52,86	5,48	10,87
(X)	H	t-C_4H_9	Gly	94,0	–	0,30 C	44,67	6,72	9,31	$C_{11}H_{20}Cl_2N_2O_3$	44,15	6,74	9,36
(XI)	C_4H_9	t-C_4H_9	L-Leu	95,2	–	0,68 C	50,92	7,89	7,85	$C_{15}H_{28}Cl_2N_2O_3$	50,70	7,94	7,88
(XII)	C_4H_9	t-C_4H_9	L-Ileu	97,8	+5,77	0,64 C	51,00	7,92	7,85	$C_{15}H_{28}Cl_2N_2O_3$	50,70	7,94	7,88
(XIII)	$CH_2C_6H_5$	t-C_4H_9	L-Phe	98,0	+2,65	0,50C	55,49	7,67	6,93	$C_{18}H_{28}Cl_2N_2O_3$	55,52	6,76	7,19
(XIV)	$CH_2COOC_4H_9$-t	t-C_4H_9	L-Asp	92,5	−7,50	0,68 C	49,49	7,29	6,78	$C_{17}H_{30}Cl_2N_2O_5$	49,39	7,31	6,77

*Systems for TLC: A = 10:1 ether—methanol; B = 4: 1 ether—hexane; C = ether.

CONCLUSIONS

A convenient method was proposed for the preparation of the alkyl esters of N,N-bis(2-chloroethyl)carbamoyl-α-amino acids.

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SOME ONE-ELECTRON OXIDATION REACTIONS OF BIHETEROORGANIC DERIVATIVES WITH Ge—Hg AND Ge—Li GROUPINGS

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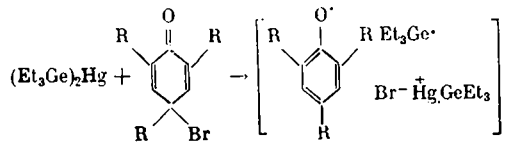
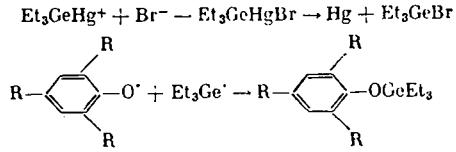
Bis(triethylgermyl)mercury (I) reacts with substituted o-quinones and 4-bromo-2,4,6-tri-tert-butylcyclohexadien-2,5-one (II) by the one-electron transfer mechanism to give paramagnetic particles in the intermediate step of the process [1, 2].

A blue color appears and the formation of mercury is observed when a hexane solution of (I) is added slowly to (II). The EPR signal, belonging to the 2,4,6-tri-tert-butylphenoxyl radical (III), disappears when the Hg ceases to deposit. The main reaction products are Hg (94%), triethylbromogermane (~100%), and 1-triethylgermyloxy-2,4,6-tri-tert-butylbenzene (IV) (77%), the formation of which can be depicted by the following scheme:



(I) (II)

$$Et_3GeHg^+ + Br^- \rightarrow Et_3GeHgBr \rightarrow Hg + Et_3GeBr$$



(III) (IV) R=C(CH3)3

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