SYNTHESIS OF DI(2-CHLOROETHYL)AMINOCYCLOHEXYLCARBOXYLIC (ACETIC) ACIDS AND THEIR DERIVATIVES

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The acylation of amino acids and peptides by di(2-chloroethyl)aminophenylalkanoic acids lowered the toxicity of the starting cytostatic phenylalkanoic acids, which made it possible to obtain compounds (lophenal, etc.) with a high selective effect [1, 2]. Up to now the di(2-chloroethyl)aminocyclohexylalkanoic acids, the structural analogs of the p-[di(2-chloroethyl)amino]phenylalkanoic acids, have received little study. Data are also lacking in the literature on the toxicity and antitumor activity of amino acids and peptides, acylated by di(2-chloroethyl)aminocyclohexylcarboxylic (CHC) and di-(2-chloroethyl)aminocyclohexylacetic (CHA) acids. In addition, the inactivation of the di(2-chloroethyl)amino group in the above indicated compounds by their oxidation to the N-oxide converts the cytotoxic grouping to the latent state, which can exert an important effect on the therapeutic properties of the compounds.

In the present paper, in order to obtain compounds with a latent effect, we synthesized the cis-3- and cis-4-[di(2-chloroethyl)amino]CHC, cis-4-[di(2-chloroethyl)amino]CHA, their esters, the N-oxide of the ethyl ester of cis-4-[di(2-chloroethyl)amino]CHA, and also DL-phenylalanine and DL-valine, containing N-acylated cis-4-[di(2-chloroethyl)amino]CHA.

4-[Di(2-chloroethyl)amino]CHC was synthesized previously [3], but the stereoconfiguration of the 4-amino-CHC, which apparently represented a mixture of the cis and trans isomers, was not taken into consideration in its synthesis. In the present paper the pure cis isomers of the ethyl ester of the 3- and 4-amino-CHC and 4-amino-CHA [4, 5] served as the starting compounds for the synthesis of the mentioned compounds. The hydroxyethylation of these compounds in aqueous solution gave the ethyl esters of the cis-3- and cis-4-[di(2-hydroxyethyl)amino]CHC (I) and (II), and of cis-4-[di(2-hydroxyethyl)amino]CHA (III), which then were reacted as such with excess $SOCl_2$. The formed hydrochlorides of the ethyl esters of the cis-3- and cis-4-[di(2-chloroethyl)amino]CHC (IV) and (V), and of cis-4-[di(2-chloroethyl)amino]CHA (VI), when hydrolyzed with conc. HCl were converted to the hydrochlorides of the cis-3- and cis-4-[di(2-chloroethyl)amino]CHC (VII) and (VIII), and of cis-4-[di(2-chloroethyl)amino]CHA (IX). Treatment of hydrochlorides (VI), (VII), and (IX) with EtONa gave cis-3-[di(2-chloroethyl)amino]CHC (X), cis-4-[di(2-chloroethyl)amino]CHA (XI), and the ethyl ester of cis-4-[di(2-chloroethyl)amino]CHA (XII). The oxidation of the latter with excess perbenzoic acid in chloroform gave the N-oxide of the ethyl ester of cis-4-[di(2-chloroethyl)amino]CHA (XIII).

We used the carbodiimide method to synthesize the DL-phenylalanine and DL-valine derivatives, acetylated with cis-4-[di(2-chloroethyl)amino]CHA. The benzyl and benzhydryl esters were selected as the C-protective group in the amino acids. It should be mentioned that the benzyl ester of DL-phenylalanine failed to condense with cis-4-[di(2-chloroethyl)-amino]CHA (XI) in the presence of 1,3-dicyclohexylcarbodiimide (DCHC) and the starting products were recovered unchanged. Apparently, in $CHCl_3$ solution the H atom of the carboxyl group of cis-4-[di(2-chloroethyl)amino]CHA protonates the N atom of the di(2-chloroethyl)-amino group to give a stable salt, as a result of which acid (XI) is incapable of reacting with the DCHC. Consequently, we used the hydrochloride of cis-4-[di(2-chloroethyl)amino]CHA (IX), the condensation of which with either the benzyl or benzhydryl ester of DL-phenylalanine and DL-valine in the presence of DCHC gave the hydrochlorides of the benzyl and benzhydryl esters of N-cis-4-[di(2-chloroethyl)aminocyclohexylacetyl-DL-phenylalanine and N-cis-4-(di-2-chloroethyl)aminocyclohexylacetyl-DL-valine, (XIV)-(XVII). The catalytic

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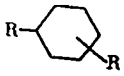
TABLE 1. cis-3- and cis-4-[Di(2-chloroethyl)amino]CHC, cis-4-[Di(2-chloroethyl)amino]CHA, and Their Derivatives



Compound	R	R'	Recrystallization solvent	mp., °C	Yield, %	Found, %		Empirical formula	Calc., %	
						N	Cl		N	Cl
(I)	$(OHCH_2CH_2)_2N$	3-$COOC_2H_5$	–	Oil	80	5,21	–	$C_{13}H_{25}NO_4$	5,40	–
(II)	The same	4-$COOC_2H_5$	–	»	52	5,72	–	$C_{13}H_{25}NO_4$	5,40	–
(III)	»	4-$CH_2COOC_2H_5$	–	»	90	5,29	–	$C_{14}H_{27}NO_4$	5,12	–
(IV)	$(ClCH_2CH_2)_2N \cdot HCl$	3-$COOC_2H_5$	Methanol–ether	134–137	86	4,00	31,80	$C_{13}H_{24}NO_2Cl_3$	4,21	32,00
(V)	The same	4-$COOC_2H_5$	Isopropanol	160–163	44	4,26	32,32	$C_{13}H_{24}NO_2Cl_3$	4,21	32,00
(VI)	»	4-$CH_2COOC_2H_5$	Ethyl acetate	138–140	75	4,22	30,85	$C_{14}H_{26}NO_2Cl_3$	4,03	30,67
(VII)	»	3-COOH	Methanol–petroleum ether	85*	86	4,75	35,20	$C_{11}H_{20}NO_2Cl_3$	4,59	34,89
(VIII)	»	4-COOH	Isopropanol	177–180	89	4,62	35,08	$C_{11}H_{20}NO_2Cl_3$	4,59	34,89
(IX)	»	4-CH_2COOH	Abs. ethanol – abs. ether	57–60	80	4,20	33,00	$C_{12}H_{22}NO_2Cl_3$	4,39	33,37
(X)	$(ClCH_2CH_2)_2N$	3-COOH	Methanol	109–111	85	4,99	26,17	$C_{11}H_{19}NO_2Cl_2$	5,22	26,44
(XI)	The same	4-CH_2COOH	Abs. ethanol – abs. ether	64–70*	72	5,19	24,80	$C_{12}H_{21}NO_2Cl_2$	4,96	25,12
(XII)	The same	4-$CH_2COOC_2H_5$	–	Oil	90	4,81	22,65	$C_{14}H_{25}NO_2Cl_2$	4,51	22,85
(XIII)	$(ClCH_2CH_2)_2N$	The same	Acetone	163–166	33	4,44	22,27	$C_{14}H_{25}NO_3Cl_2$	4,29	21,73
(XIV)	$(ClCH_2CH_2)_2N \cdot HCl$	4-$CH_2CONHCHCOOCH_2C_6H_5$ $CH_2C_6H_5$	Ethanol	120*	68	4,81	19,35	$C_{28}H_{37}N_2O_3Cl_3$	5,03	19,13
(XV)	The same	4-$CH_2CONHCHCOOCH_2C_6H_5$ $CH_2(CH_3)_2$	–	Oil	90	5,23	21,10	$C_{24}H_{37}N_2O_3Cl_3$	5,51	20,94
(XVI)	»	4-$CH_2CONHCHCOOCH(C_6H_5)_2$ $CH_2C_6H_5$	Ethanol –ether	82–89*	50	4,28	16,81	$C_{34}H_{41}N_2O_3Cl_3$	4,43	16,82
(XVII)	»	4-$CH_2CONHCHCOOCH(C_6H_5)_2$ $CH(CH_3)_2$	Chloroform–petroleum ether	67–73*	70	5,09	18,13	$C_{30}H_{41}N_2O_3Cl_3$	4,79	18,21
(XVIII)	»	4-$CH_2CONHCHCOOH$ $CH_2C_6H_5$	Ethanol –ether	98*	a) 85 b) 62	6,04	22,87	$C_{21}H_{31}N_2O_3Cl_3$	6,01	22,83
(XIX)	»	4-$CH_2CONHCHCOOH$ $CH(CH_3)_2$	The same	66–74*	a) 61 b) 92	6,91	25,30	$C_{17}H_{31}N_2O_3Cl_3$	6,70	25,45

*Melts with decomposition.

hydrogenolysis of benzyl esters (XIV) and (XV) over Pd black, and the cleavage of the benzhydryl protective group in (XVI) and (XVII) with HCl in glacial AcOH, gave the hydrochlorides of N-cis-4-[di(2-chloroethyl)amino]cyclohexylacetyl-DL-phenylalanine and N-cis-4-[di(2-chloroethyl)amino]cyclohexylacetyl-DL-valine, (XVIII) and (XIX). The properties of compounds (I)-(XIX) are given in Table 1.

EXPERIMENTAL

Ethyl Ester of cis-4-[Di(2-hydroxyethyl)amino]CHA (III). To 11.1 g (0.06 mole) of the ethyl ester of cis-4-amino-CHA in 15 ml of water was added 9 ml (0.18 mole) of ethylene oxide. The mixture was cooled, let stand overnight, and then it was vacuum-distilled. The residue was dried by the azeotropic distillation of the water with benzene. The residual oil was dissolved in abs. ethanol, filtered, and the solvent was evaporated in vacuo. The oily residue was dried in a vacuum-desiccator to give 15 g of (III).

Esters (I) and (II) were obtained in a similar manner.

Hydrochloride of Ethyl Ester of cis-4-[Di(2-chloroethyl)amino]CHA (VI). With stirring and cooling, to 15 g (0.05 mole) of ethyl ester (III) in 30 ml of $CHCl_3$ was added 24 ml (0.32 mole) of $SOCl_2$ in 1 h, the mixture was kept for 1 h at ~20°C, and then it was heated for 30 min on the water bath. The solvent and excess $SOCl_2$ were vacuum-distilled. The oily residue was dissolved in benzene, cooled, and poured into chilled petroleum ether to give 13.5 g of (VI).

Ethyl ester hydrochlorides (IV) and (V) were obtained in a similar manner.

Hydrochloride of cis-4-[Di(2-chloroethyl)amino]CHA (IX). To 2.3 g of ethyl ester hydrochloride (VI) was added 12 ml of conc. HCl and the mixture was heated for 1.5 h in an oil bath. The excess HCl was vacuum-distilled, while the residual oil was dried by the azeotropic distillation of the water with benzene. The residue was dissolved in abs. ethanol and poured into chilled petroleum ether. The obtained oily residue was dried in a vacuum-desiccator to give 1.6 g of (IX).

Hydrochlorides (VII) and (VIII) were obtained in a similar manner.

cis-4-[Di(2-chloroethyl)amino]CHA (XI). To 1 g (exact weight) of hydrochloride (IX) in 4 ml of abs. ethanol was added 5.25 ml (equivalent amount) of 0.587 N EtONa solution. The reaction mixture was let stand overnight in the refrigerator, the filtrate was treated with active carbon, and then abs. ether was added. The obtained oil was rubbed in abs. ether to a powdery state and dried in a vacuum-desiccator (hygroscopic substance). We obtained 0.64 g of (XI).

Compound (X) and ethyl ester (XII) were obtained in a similar manner.

N-Oxide of Ethyl Ester of cis-4-[Di(2-chloroethyl)amino]CHA (XIII). With cooling, to 3.73 g (0.012 mole) of (XII) in 10 ml of $CHCl_3$ was gradually added 3.3 g (0.024 mole) of perbenzoic acid in 50 ml of $CHCl_3$, the mixture was let stand overnight, the solvent was evaporated in the air, the residue was treated in the cold with 5% ammonia water, the mixture was extracted with ether, the ether layer was washed with water, dried over $MgSO_4$, and the solvent was vacuum-distilled (without heat). The oily residue was recrystallized from acetone to give 1.24 g of (XIII).

Hydrochloride of Benzyl Ester of N-cis-4-[Di(2-chloroethyl)amino]cyclohexylacetyl-DL-phenylalanine (XIX). To 4.61 g of hydrochloride (IX) in $CHCl_3$ were added 2.98 g of DCHC in $CHCl_3$ and 3.7 g of the benzyl ester of DL-phenylalanine in $CHCl_3$, the mixture was let stand overnight, the dicyclohexylurea was filtered, the solvent was evaporated in vacuo, and the residue was recrystallized from ethanol to give 5.4 g of (XIV).

Hydrochlorides (XV)-(XVII) were obtained in a similar manner.

Hydrochloride of N-cis-4-[Di(2-chloroethyl)amino]cyclohexylacetyl-DL-phenylalanine (XVIII). a) A solution of 2.65 g of (XIV) in 50 ml of ethanol was shaken in an H_2 atmosphere over Pd black until the H_2 absorption ceased. The catalyst was filtered, the solvent was evaporated in vacuo, and the residue was rubbed in abs. ether and dried in a vacuum-desiccator to give 2 g of (XVIII).

Hydrochloride (XIX) was obtained in a similar manner.

b) A solution of 0.06 g of (XVI) in 5 ml of HCl-saturated glacial AcOH was kept for 3 days at ∿20°. The obtained white crystalline precipitate was filtered, dissolved in abs. ethanol, and precipitated with abs. ether. After drying in a vacuum-desiccator we obtained 0.25 g of (XVIII), which was identical with the product obtained by method a).

Hydrochloride (XIX) was obtained in a similar manner.

CONCLUSIONS

1. We synthesized the cis-3-[di(2-chloroethyl)amino]cyclohexylcarboxylic, cis-4-[di-(2-chloroethyl)amino]cyclohexylcarboxylic, and cis-4-[di-(2-chloroethyl)amino]cyclohexylacetic acids, and also their ethyl esters, both as the hydrochlorides and as the free bases.

2. The acylation of the esters of DL-phenylalanine and DL-valine by the carbodiimide method proceeds only in the case where the amino group of cis-4-[di-(2-chloroethyl)amino]-cyclohexylacetic acid is protonated. The hydrochlorides of N-cis-4-[di-(2-chloroethyl)-amino]cyclohexylacetyl-DL-phenylalanine and N-cis-4-[di-(2-chloroethyl)amino]cyclohexylacetyl DL-valine were synthesized by removing the benzyl and benzhydryl C-protective groups from the corresponding esters.

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