SYNTHESIS OF OPTICAL ANTIPODES OF N-p-[DI-(2-CHLOROETHYL)AMINO]PHENACETYLAMINO ACIDS

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The antitumorigenic properties of certain compounds depend on their optical configuration. Thus, the L-antipode of p-[di-(2-chloroethyl)amino]phenylalanine is more active than the racemate of sarcolysine and the D-isomer [1]. N-p-[Di-(2-chloroethyl)amino]phenacetylamino acids (DChAPhA) are more active and less toxic than p-[di-(2-chloroethyl)amino]phenylacetic acid [2]. However, racemic phenylalanine, alanine, methionine, and glutamic acid acylated with p-[di-(2-chloroethyl)amino]phenylacetic acid (DChAPhAC) are recommended for clinical study.

The synthesis of optical antipodes of N-p-[di-(2-chloroethyl)amino]phenylacetylvaline, alanine, and methionine is described in this paper and racemization during their synthesis of carbodiimide, acid chloride, cyanomethyl, and N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline methods was studied. Benzhydryl esters of amino acids were obtained without racemization by condensation of the latter with diphenylidiazomethane [3]. Removal of the protecting group was achieved at room temperature by reaction of HCl in glac. CH_3COOH. It was shown chromatographically that complete cleavage of the benzhydryl radical occurs in 12 h. To establish the degree of racemization during synthesis the optical activity of the obtained compounds and optically pure N-acylamino acids, which were obtained via the azide of DChAPhAs, was compared.

It is seen from results presented in Table 1 that the most suitable methods of synthesizing L- and D-DChAPhA were the acid chloride and N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline methods, giving high yields and optical purity of the obtained antipodes. During synthesis by the carbodiimide method the optical purity of the antipodes is lower, although the total yield of products is not decreased. The use of activated cyanomethyl esters for their synthesis leads to racemic compounds.

EXPERIMENTAL METHOD

$[\alpha]_D$ of the compounds was measured on a Perkin–Elmer 141M polarimeter; melting points were determined on a Koffler microheating table. Purity of products was confirmed by the method of TLC on plates having a fixed layer of silica gel with $CHCl_3$ as the eluent.

DChAPhA was obtained by the acid chloride method from the corresponding antipode of the amino acid and the acid chloride of DChAPhAc analogously to [4] [see Table 1, compounds (I)–(VI)]. * Upon using the carbodiimide method equimolar amounts of the benzhydryl ester of the corresponding amino acid in THF were condensed with DChAPhAc using 1,3-dicyclohexylcarbodiimide. Benzhydryl esters of DChAPhA were separated from ethanol and recrystallized [see Table 1, compounds (VII)–(IX)].†

* N-p-[Di-(2-chloroethyl)amino]phenacetyl-L- and D-methionine were separated from ethanol as the cyclohexylammonium salt.

† Benzhydryl esters of N-p-[di-(2-chloroethyl)amino]phenacetyl-L-valine and L-alanine were separated as oils, which were purified by passing through a column of SiO_2 in chloroform.

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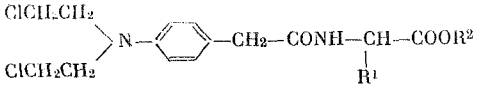
TABLE 1



Compound	R^1	R^2	Method of synthesis	Yield, %	Configuration	$[\alpha]_D^{20}$ C1, $CHCl_3$	Optical purity, %	mp, °C (solvent)	Found, % C	Found, % H	Found, % N	Empirical formula	Calc. % C	Calc. % H	Calc. % N
(I)	$CH(CH_3)_2$	H	Acid chloride	60	*L*	+21,2	98	51—52 (benzene)	54,16	6,23	7,21	$C_{17}H_{24}Cl_2N_2O_3$	54,40	6,45	7,47
(II)	$CH(CH_3)_2$	H		60	*D*	−21,0	97	51—52 (benzene)	54,17	6,34	7,26	$C_{17}H_{24}Cl_2N_2O_3$	54,40	6,45	7,47
(III)	CH_3	H		58	*L*	+12	95	89—90 (benzene)	52,14	5,72	7,93	$C_{15}H_{20}Cl_2N_2O_3$	51,90	5,81	7,89
(IV)	CH_3	H		58	*D*	−11,8	93	89—90 (benzene)	51,18	5,66	8,11	$C_{15}H_{20}Cl_2N_2O_3$	51,90	5,81	7,89
(V)	$(CH_2)_2SCH_3$	$H \cdot NH_2C_6H_{11}$		50	*L*	+8,5	94	112 (ethyl acetate)			8,39	$C_{23}H_{37}Cl_2N_3SO_3$			8,48
(VI)	$(CH_2)_2SCH_3$	$H \cdot NH_2C_6H_{11}$		50	*D*	−8,7	96	112 (ethyl acetate)			8,58	$C_{23}H_{37}Cl_2N_3SO_3$			8,48
(VII)	$CH(CH_3)_2$	H	Carbodiimide	60	*L*	+18,2	84	51—52 (benzene)			7,35	$C_{17}H_{24}Cl_2N_2O_3$	54,40	6,45	7,47
(VIII)	$(CH_2)_2SCH_3$	$CH(C_6H_5)_2$		90	*L*	−8,4	83	64—66 (ethanol)	61,52	6,03	5,09	$C_{30}H_{34}Cl_2N_2SO_3$	61,74	5,87	4,88
(IX)	$(CH_2)_2SCH_3$	$CH(C_6H_5)_2$		86	*D*	+8,0	79	64—66 (ethanol)	62,48	5,96	4,77	$C_{30}H_{34}Cl_2N_2SO_3$	61,74	5,87	4,88
(X)	$(CH_2)_2SCH_3$	$H \cdot C_6H_{11}NH_2$		70	*L*	+6,7	74	111—112(ethyl acetate)	54,87	7,33	8,61	$C_{23}H_{37}Cl_2N_3SO_3$	54,60	7,37	8,48
(XI)	$(CH_2)_2SCH_3$	$H \cdot C_6H_{11}NH_2$		66	*D*	−6,2	70	111—112(ethyl acetate)	54,39	7,42	8,51	$C_{23}H_{37}Cl_2N_3SO_3$	54,60	7,37	8,48
(XII)	$CH(CH_3)_2$	H	N-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline	80	*L*	+24,0	97	51—52 (benzene)			7,65	$C_{17}H_{24}Cl_2N_2O_3$			7,47
(XIII)	$(CH_2)_2SCH_3$	$CH(C_6H_5)_2$		70	*D*	+9,8	97	64—66 (ethanol)			4,95	$C_{30}H_{34}Cl_2N_2SO_3$			4,88
(XIV)	$(CH_2)_2SCH_3$	$H \cdot C_6H_{11}NH_2$		65	*D*	−8,8	97	112 (ethyl acetate)			8,62	$C_{23}H_{37}Cl_2N_3SO_3$			8,48
(XV)	$CH(CH_3)_2$	H	Activated cyanomethylesters	52	*DL*	0	0	51—55 (benzene)			7,29	$C_{17}H_{24}Cl_2N_2O_3$			7,47
(XVI)	CH_3	H		44	*DL*	0	0	85—90 (benzene)			8,01	$C_{15}H_{20}Cl_2N_2O_3$			7,89
(XVII)	$CH(CH_3)_2$	H	Azide	51	*L*	+21,6	100	51—52 (benzene)			7,32	$C_{17}H_{24}Cl_2N_2O_3$			7,47
(XVIII)	$(CH_2)_2SCH_3$	$CH(C_6H_5)_2$		36	*L*	−10,1	100	65—66 (ethanol)			4,72	$C_{30}H_{34}Cl_2N_2SO_3$			4,88
(XIX)	$(CH_2)_2SCH_3$	$H \cdot C_6H_{11}NH_2$		33	*L*	+9,0	100	112 (ethyl acetate)			8,63	$C_{23}H_{37}Cl_2N_3SO_3$			8,48
(XX)	CH_3	H		30	*L*	+12,6	100	90 (benzene)			8,03	$C_{15}H_{20}Cl_2N_2O_3$			7,89

To remove the benzhydryl groups 0.01 mole of the benzhydryl ester of DChAPhA was treated at ~ 20° with 20 ml of glac. CH_3COOH saturated with HCl and left overnight. The mixture was evaporated in vacuum; the residue was dissolved in 30 ml of methanol and poured into an aqueous solution of CH_3COONa. The precipitated oil was extracted with $CHCl_3$ and dried over $MgSO_4$. The filtrate was evaporated in vacuum and the residue was recrystallized [see Table 1, compounds (VII), (X)—(XII), (XIV)—(XVII), (XIX), (XX)].

Upon using the N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline method to a solution of 0.02 mole of DChAPhAc and 0.02 mole of benzhydryl ester of the corresponding amino acid in 35 ml of abs. THF with stirring was added 0.02 mole of N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline [5]. The reaction mixture was mixed for 8 h at 30-40° and left overnight at ~ 20°. The THF was evaporated in vacuum and the obtained benzhydryl esters of DChAPhA were recrystallized [see Table 1, compounds (XII), (XIII)].

Upon obtaining DChAPhA by the azide method 0.01 mole of DChAPhAc hydrazide [6] was dissolved in 30 ml of glac. CH_3COOH, 75 ml of water was added, and the mixture was cooled in ice. Then 3 ml of conc. HCl and a solution of 0.081 g of $NaNO_2$ in 5 ml of water were added. The precipitated oil was extracted with cold ethyl acetate, washed with cold saturated $NaHCO_3$ solution, water, and then with 0.01 N HCl and water, dried with $MgSO_4$ at 0°, and filtered. To the filtrate was added a solution of 0.01 mole of benzhydryl ester of the amino acid in ethyl acetate and the reaction mixture was left in the refrigerator for 72 h. The solution was washed with 0.1 N HCl, saturated $NaHCO_3$ solution, water, and dried over $MgSO_4$. The ethyl acetate was evaporated in vacuum and the residue was recrystallized [see Table 1, compounds (XVII), (XVIII), (XX)].

Upon using the activated cyanomethyl ester method 0.01 mole of the cyanomethyl ester of DChAPhA-(DChAPhC) in 10 ml of THF was added with stirring to a solution of 0.01 mole of benzhydryl ester of the amino acid in 10 ml of THF containing 2 drops of glac. CH_3COOH. The reaction mixture was left at 20° for 48 h, the THF was evaporated in vacuum, and the residue was dissolved in ethyl acetate. The solution was washed with 0.01 N HCl, cold 3% $NaHCO_3$, water, and dried over $MgSO_4$. The filtrate was evaporated in vacuum and the residue was recrystallized [see Table 1, compounds (XV), (XVI)].

To obtain DChAPhC 0.02 mole of DChAPhA was mixed with 4.16 ml of triethylamine and 3.82 g of chloroacetonitrile was added. The reaction mixture was maintained for 30 min at 70°, then left overnight. After adding 30 ml of ethyl acetate the triethylamine hydrochloride was filtered. The filtrate was evaporated in vacuum and the residue was recrystallized twice from ethanol. We obtained 4.7 g of DChAPhC with mp 35-37°, yield 75%. Found: C 53.43; H 5.32; Cl 21.90; N 8.89%. $C_{14}H_{16}Cl_2N_2O_2$. Calculated: C 53.38; H 5.15; Cl 22.6; N 8.94%.

CONCLUSIONS

The optical antipodes of N-p-[di-(2-chloroethyl)amino]phenacetylvaline, methionine, and alanine were obtained by the acid chloride and N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline methods; the carbodiimide method and the activated cyanomethyl ester method give significant or complete racemization.

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