SYNTHESIS OF CARBOCYCLOHEXYLOXYAMINO ACIDS

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Previously, it had been reported that in the peptide synthesis it is possible in a number of cases to use carbocyclohexyloxy protection (CChO-)* [1], which has a number of valuable advantages. Thus, it is removed in hydrobrominolysis and is stable during catalytic hydrogenation. Besides this, we established that the CChO amino acids are obtained in higher yields than, for example, in the case of the carbobenzoxyamino acids, and they also crystallize with much greater ease than the latter [2]. This also applies to such amino acids as proline, leucine, valine, phenylalanine, etc. The cleavage of the CChO group does not go very fast [1], which hinders its use to a substantial degree. Previously the theory was expressed that the nature of the amino-acid radical can affect its rate of cleavage during hydrobrominolysis [3]. To study this problem we synthesized a number of CChO amino acids (table) by a procedure closely similar to that used to obtain the corresponding carbobenzoxy derivatives.

EXPERIMENTAL

CChO-Dl-alanine (I). To a solution of 2 g of DL-alanine in 15 ml of 2 N NaOH solution at 0° was added in portions, with stirring, 4 g of carbocyclohexyl chloride (CChO-Cl) in an hour; the pH of the medium (8-9) was controlled by the addition of 15 ml of 4 N NaOH solution. The stirring was continued for another 1-1.5 h at 20°, after which the reaction mixture was extracted with ether and the alkaline layer was acidified with 6 N HCl; the obtained oil crystallized on cooling. We obtained 4.2 g (87%) of (I); m. p. 123-125°. CChO-L-phenylalanine, CChO-DL-methionine and CChO-L-tyrosine were obtained in a similar manner (see table).

CChO-DL-leucine (II). To a solution of 3 g of DL-leucine in 12 ml of 2 N NaOH at 0° were added in an hour, in portions, 4 g of CChO-Cl and 14 ml of 2 N NaOH. The reaction mass was stirred for another hour at 20°, after which it was washed with ether and the aqueous layer was acidified with 6 N HCl. The obtained oil was extracted with ethyl acetate, and the solutions was dried over Na_2SO_4 and evaporated. The obtained oily residue was dissolved in 15 ml of 20% $KHCO_3$ solution and the solution was acidified with concd. HCl. The obtained oil was extracted with ethyl acetate (4 × 25 ml) and the solution was dried over Na_2SO_4, evaporated, and the obtained oil became crystalline when kept over P_2O_5 in vacuo. We obtained 4.13 g (70%) of (II); m. p. 78-80°. CChO-L-proline and CChO-DL-valine were obtained in a similar manner (see table).

CChO-DL-serine (III). To a solution of 1.5 g of DL-serine in 30 ml of saturated $NaHCO_3$ solution was added 2.4 g of CChO-Cl. The reaction mixture was stirred vigorously for 2 h at 25°, after which the solution was washed with ether. Acidification with concd. HCl gave 2.8 g (85%) of (III); m. p. 105-107°. CChO-DL-threonine was obtained in a similar manner (see table).

CChO-DL-aspartic acid (IV). A mixture of 3.25 g of DL-aspartic acid, 3 g of MgO, 40 ml of water and 13 ml of ether was stirred at 0°. Then 5.2 g of CChO-Cl was added in portions over 30 min, after which the mixture was kept at 20° for 1 h, the MgO was filtered off, and the solution was extracted with ether and then acidified with concd. HCl. The obtained oil was extracted with ethyl acetate, and the solution was dried over Na_2O_4 and then evaporated in vacuo. The residual oil was reprecipitated from ethyl acetate solution with petroleum ether, and the obtained

* $\overline{\text{CChO}}-=\langle\bigcirc\rangle-O-CO-$.

Carbocyclohexyloxy derivatives of α-amino acids	Empirical formula and mol. wt.	Found, %		Calcd., %		Yield, %	M. p., °C
		H	C	H	C		
DL-Alanine [1]	$C_{10}H_{17}O_4N$ 215	8,21	55,40	8,28	55,81	92	124--125*
DL-Valine	$C_{12}H_{21}O_4N$ 243	8,61	59,00	8,64	59,26	70	68--90 *
DL-Leucine	$C_{13}H_{23}O_4N$ 257	8,86	60,61	8,95	30,70	95	78--80 *
DL-Serine	$C_{10}H_{17}O_5N$ 231	7,48	52,28	7,36	51,95	80	105--107*
DL-Threonine	$C_{11}H_{19}O_5N$ 245	8,0	53,77	7,75	53,88	82	133--134*
L-Phenylalanine [1]	$C_{16}H_{21}O_4N$ 291	7,16	66,21	7,22	65,98	94	133--136*
L-Tyrosine	$C_{16}H_{21}O_5N$ 307	6,75	62,31	6,84	62,54	86	154--155*
L-Proline	$C_{12}H_{19}O_4N$ 241	7,85	59,53	7,88	59,75	87	82--83 *
DL-Methionine* [1]	$C_{11}H_{19}O_4SN$ 261	7,23	50,39	7,27	50,57	82	99--101*
DL-Aspartic acid	$C_{11}H_{17}O_6N$ 259	6,63	50,71	6,56	50,96	50	139--141*
L-Glutamic acid	$C_{12}H_{19}O_6N$ 273	6,79	52,58	6,96	52,75	44	105--107*
DL-Aminoadipic acid	$C_{13}H_{21}O_6N$ 287	7,22	54,11	7,32	54,36	40	85--87 *

*From water.

oil crystallized on cooling and rubbing. We obtained 3.18 g (50%) of (IV); m. p. 139-141°. CChO-L-glutamic acid and CChO-DL-aminoadipic acid were obtained in a similar manner (see table).

SUMMARY

The carbocyclohexyloxy derivatives of some α-amino acids were synthesized.

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