6. B. A. Arbuzov, A. V. Fuzhenkova, and G. A. Tudrii, Izv. Akad. Nauk SSSR, Ser. Khim., 1976, 2369.
7. A. N. Pudovik, I. V. Konovalova, and É. A. Ishmaeva, Reactions and Methods for the Investigation of Organic Compounds [in Russian], Vol. 23, Khimiya (1973).
8. B. A. Arbuzov, G. A. Tudrii, and A. V. Fuzhenkova, Izv. Akad. Nauk SSSR, Ser. Khim., 1979, 1585.
9. B. A. Arbuzov, A. V. Fuzhenkova, G. A. Tudrii, and V. M. Zoroastrova, Izv. Akad. Nauk SSSR, Ser. Khim., 1975, 1391.
10. B. A. Arbuzov, O. D. Zolova, V. S. Vinogradova, and Yu. Yu. Samitov, Dokl. Akad. Nauk SSSR, 173, 335 (1967).
11. D. Gorenstein and F. H. Westheimer, J. Am. Chem. Soc., 92, 634 (1970).
12. K. Igbal and W. R. Jackson, J. Chem. Soc. C, 1968, 616.

PHENYLALANINE DERIVATIVES CONTAINING ACYL GROUPS OF STEREOISOMERIC N-[TETRAMETHYLDIAMIDO(THIO)PHOSPHORYL]- AND N-[DIMORPHOLIDO(THIO)PHOSPHORYL]-4-AMINOCYCLOHEXANE-CARBOXYLIC ACIDS

L. A. Patotskene, K. I. Karpavichyus,
and I. L. Knunyants

UDC 542.91:547.586.2:547.1'118

Guided by the interest attaching to the antitumor activity of the nonalkylating tetraalkyldiamidophosphoryl derivatives of cyclohexylamine, morpholine, and 4-aminocyclohexanecarboyxlic acid (ACHCA) [2], we have continued our earlier work on the biological properties of the stereoisomeric N-[diethyleneimido(thio)-phosphoryl]aminocyclohexylcarbonyl amino-acids [1] by synthesizing certain compounds containing tetramethyldiamido(thio)phosphoryl and dimorpholido(thio)phosphoryl groups.

Synthesis was carried out by using dicyclohexylcarbodiimide (DCHC) to condense N-phthaloyl-cis- and N-phthaloyl-trans-4-ACHCA with the ethyl ester of DL-phenylalanine. Each of these isomers reacted equally well under the conditions in question here. The protective N-phthaloyl groups in the N-phthaloyl-cis- and N-phthaloyl-trans-4-ACHC*-DL-phenylalanine ethyl esters were eliminated by treatment with hydrazine hydrate in CH_2Cl_2–alcohol solution at 40°C. PMR studies showed that complete elimination, without byproduct formation, could be attained in 15 h. The final reaction products, the stable salts of the ethyl esters of trans- and cis-4-ACHC-DL-phenylalanine with phthaloyl hydrazide, were broken down in alcoholic HCl solution. These procedures gave good yields of the chlorohydrates and free bases of the ethyl esters of trans- and cis-4-ACHC-DL-phenylananine which could, in turn, be converted to the ethyl esters of N-dichloro(thio)phosphoryl-trans- and cis-4-ACHC-DL-phenylalanine by the method described in [1].

The ethyl esters of N-tetramethyldiamido(thio)phosphoryl-trans- and cis-4-ACHC-DL-phenylalanine (I), (II), (IX), and (X) were obtained by reacting the dichlorohydrides with excess dimethylamine in solution in inert solvents. The ethyl esters of N-dimorpholido(thio)phosphoryl-trans- and cis-4-ACHC-DL-phenylalanine, (III), (IV), (XI), and (XII), were obtained by condensing the ethyl esters of N-dichloro(thio)phosphoryl-trans- and cis-4-ACHC-DL-phenylalanine with morpholine in the presence of triethylamine.

Hydrolysis of the ethyl esters (I)-(IV) and (X)-(XII) by the theoretical amount of MeONa in aqueous solution gave good yields of the sodium salts of N-tetramethyldiamido(thio)phosphoryl-trans-, N-dimorpholido-(thio)trans-, and cis-4-ACHC-DL-phenylalanine, (V)-(VIII) and (XIII)-(XV), as stable, water-soluble compounds. The characteristics of these compounds are summarized in Tables 1 and 2.

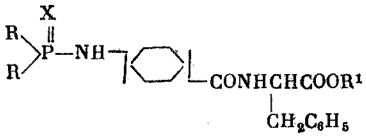
---

*ACHC designates aminocyclohexylcarbonyl.

Institute of Heteroorganic Compounds, Academy of Sciences of the USSR, Moscow. Institute of Biochemistry, Academy of Sciences of the Lithuanian SSR, Vilnius. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 2, pp. 386-390, February, 1980. Original article submitted December 14, 1978.

0568-5230/80/2902-0298$07.50

TABLE 1.



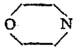
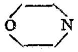
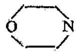
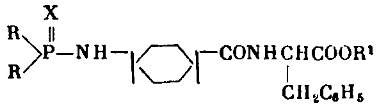
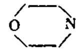
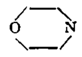
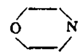
Compound	R	X	R¹	Yield, %	mp, °C	R_f	Found, %						Empirical formula	Calc., %					
							C	H	N	P	S	Na		C	H	N	P	S	Na
(I)	Me_2N	O	Et	80	200–202	0,80	58,48	8,19	12,40	7,28			$C_{22}H_{37}N_4O_4P$	58,39	8,24	12,38	6,84		
(II)	Me_2N	S	Et	69	153–156	0,89	56,47	7,89	11,94	6,72	6,92		$C_{22}H_{37}N_4O_3PS$	56,39	7,96	11,96	6,61	6,84	
(III)		O	Et	88	193–196	0,81	58,04	7,56	10,24	5,80			$C_{26}H_{41}N_4O_6P$	58,19	7,70	10,44	5,77		
(IV)		S	Et	86	200–203	0,86	56,54	7,41	10,24	5,73	5,96		$C_{26}H_{41}N_4O_5PS$	56,50	7,48	10,14	5,60	5,80	
(V)	Me_2N	O	Na	89	>253		52,15	7,64	12,15	7,04		4,82	$C_{20}H_{32}N_4O_4PNa \cdot H_2O$	51,72	7,37	12,06	6,67		4,95
(VI)	Me_2N	S	Na	91	>145		51,67	6,97	12,08	7,44	6,14	5,41	$C_{20}H_{32}N_4O_3PSNa$	51,93	6,97	12,11	6,70	6,93	4,97
(VII)		O	Na	97	>249		52,28	6,83	10,15	5,22		4,13	$C_{24}H_{36}N_4O_6PNa \cdot H_2O$	52,55	6,98	10,21	5,65		4,19
(VIII)		S	Na	66	>148		51,87	7,14	10,02	5,47	5,60	4,06	$C_{24}H_{36}N_4O_5PSNa \cdot 0{,}5H_2O$	51,88	6,71	10,08	5,57	5,77	4,14

TABLE 2.



Compound	R	X	R'	Yield, %	mp, °C	R_f	Found, %						Empirical formula	Calc., %					
							C	H	N	P	S	Na		C	H	N	P	S	Na
(IX)	Me₂N	O	Et	59	142–144	0,81	58,59	8,06	12,50	6,45			$C_{22}H_{37}N_4O_4P$	58,39	8,24	12,38	6,84		
(X)	Me₂N	S	Et	68	125–127	0,90	56,41	7,91	12,07	6,59	6,66		$C_{22}H_{37}N_4O_3PS$	56,39	7,96	11,96	6,61	6,84	
(XI)		O	Et	75	184–186	0,84	58,40	7,90	10,47	5,29			$C_{26}H_{41}N_4O_6P$	58,19	7,70	10,44	5,77		
(XII)		S	Et	92	138–141	0,91	56,60	7,56	10,20	5,32	5,58		$C_{26}H_{41}N_4O_5PS$	56,50	7,48	10,14	5,60	5,80	
(XIII)	Me₂N	S	Na	95	>144		52,08	6,94	12,29	6,35	6,66	4,62	$C_{20}H_{32}N_4O_3PSNa$	51,93	6,97	12,11	6,70	6,93	4,97
(XIV)		O	Na	96	>146		52,42	6,91	10,37	5,56		4,13	$C_{24}H_{36}N_4O_6PNa\cdot H_2O$	52,55	6,98	10,2	5,65		4,19
(XV)		S	Na	82	>138		51,93	6,89		5,56	5,43	4,13	$C_{24}H_{36}N_4O_5PSNa\cdot 0{,}5H_2O$	51,88	6,71	10,08	5,57	5,77	4,14

EXPERIMENTAL

The melting points of the various compounds were determined on a Boëtius stage; thin-layer chromatography was carried out on Al_2O_3 sheets, using a 10 : 2.5 : 2 benzene–ether–methanol mixture as eluant. The chromatograms were developed with iodine. The cis- and trans-4-ACHCA used here were pure compounds with melting points of 305 and 488-495°C (decomposition), respectively [3, 4].

Ethyl Esters of N-Phthaloyl-trans- and N-Phthaloyl-cis-4-ACHC-DL-phenylalanine. To a cooled solution containing 2.73 g of N-phthaloyl-cis-4-ACHCA dissolved in anhydrous $CHCl_3$ there was added a cooled solution containing 1.93 g of the ethyl ester of DL-phenylalanine and 2.06 g of ACHC dissolved in $CHCl_3$ and the resulting mixture allowed to stand overnight at ~20°C. The filtrate was evaporated off in vacuum; the residue was taken up in anhydrous ether, the resulting solution filtered, and the product recrystallized from ethanol solution. This procedure gave 3.85 g (86%) of the ethyl ester of N-phthaloyl-cis-4-ACHC-DL-phenylalanine, mp 169-171°C. Found: C, 69.36; H, 6.47; N, 6.23%. $C_{26}H_{28}N_2O_5$. Calculated: C, 69.63; H, 6.29; N, 6.25%.

The ethyl ester of N-phthaloyl-cis-4-ACHC-DL-phenylalanine was similarly obtained with a yield of 76%, mp 133-135°C. Found: C, 69.60; H, 6.25; N, 6.07%. $C_{26}H_{28}N_2O_5$. Calculated: C, 69.63; H, 6.29; N, 6.25%.

Salt of the Ethyl Ester of trans-4-ACHC-DL-phenylalanine with Phthaloyl Hydrazide. To a solution containing 2.24 g of the ethyl ester of N-phthaloyl-trans-4-ACHC-DL-phenylalanine dissolved in 20 ml of alcohol and 6 ml of CH_2Cl_2, there was added 0.37 g of hydrazine hydrate and the resulting mixture allowed to stand at 40°C for 15 h, at the end of which time the solvents were evaporated off in vacuum and the residue taken up in ether. This procedure gave 1.82 g (76%) of salt with melting point in excess of 273°C (from EtOH, decomposition). Found: C, 64.90; H, 6.50; N, 11.77%. $C_{26}H_{32}N_2O_5$. Calculated: C, 64.98; H, 6.71; N, 11.66%.

The salt of the ethyl ester of cis-4-ACHC-DL-phenylalanine with phthaloyl hydrazide was prepared in a similar manner; yield 69%, melting point in excess of 110°C (with decomposition). Found: C, 64.86; H, 6.59; N, 11.81%. $C_{26}H_{32}N_4O_5$. Calculated: C, 64.98; H, 6.71; N, 11.66%.

Chlorohydrate of the Ethyl Ester of trans-4-ACHC-DL-phenylalanine. A suspension of 1.2 g of the salt of the ethyl ester of trans-4-ACHC-DL-phenylalanine with phthaloyl hydrazide in 10 ml of a 0.5 N solution of HCl in anhydrous ethanol was held at ~8°C for 2 h. At the end of this time, 0.33 g (82%) of phthaloyl hydrazide with mp 339-343°C was filtered off. The filtrate was evaporated in vacuum, and the residue was triturated with ether. This procedure gave 0.64 g (84%) of the chlorohydrate of the ethyl ester of trans-4-ACHC-DL-phenylalanine, mp 130°C (with decomposition), which was identical with the material described in [1].

The chlorohydrate of the ethyl ester of cis-4-ACHC-DL-phenylalanine , similar to the material described in [1], was prepared in a similar manner; yield, 78%, mp 60°C (with decomposition).

Ethyl Ester of N-(Tetramethyldiamidophosphoryl)-trans-4-ACHC-DL-phenylalanine (I). A solution containing 4.35 g of the ethyl ester of N-(dichlorophosphoryl)-trans-4-ACHC-DL-phenylalanine [1] dissolved in 60 ml of anhydrous CH_2Cl_2 was saturated with gaseous dimethylamine at −5°C. The resulting solution was carefully washed with H_2O, dried with $MgSO_4$, evaporated in vacuum, and the residue triturated in ether. The desired compound was recrystallized from a 1 : 1 AcOEt–EtOH solution. This procedure gave 3.62 g (80%) of ester (I).

The ethyl ester of N-(tetramethyldiamidophosphoryl)-cis-4-ACHC-DL-phenylalanine (IX) was synthesized in a similar manner. The ethyl esters of N-(tetramethyldiamidothiophosphoryl)-trans-4-ACHC-DL-phenylalanine (II) and N-(tetramethyldiamidothiophosphoryl)-cis-4-ACHC-DL-phenyalanine (X) were prepared in a similar manner from N-(dichlorothiophosphoryl)-cis- and trans-4-ACHC-DL-phenylalanine, following the procedures of [1].

Ethyl Ester of N-(Dimorpholidophosphoryl)-trans-4-ACHC-DL-phenylalanine (III). A solution containing 6.52 g of the ethyl ester of N-(dichlorophosphoryl)-trans-4-ACHC-DL-phenylalanine dissolved in 30 ml of anhydrous CH_2Cl_2 was added dropwise, and with constant stirring, to a solution containing 2.61 ml of morpholine and 4.2 ml of triethylamine dissolved in 60 ml of anhydrous CH_2Cl_2 which had been cooled to −5°C. The stirring was continued for 1 h at −5°C, then for an additional 2 h at ~20°C, and the resulting mixture allowed to stand for 12 h at 8°C. At the end of this time the solution was washed with water, dried with $MgSO_4$, and the solvent evaporated off in vacuum. The residue was triturated with ether, and recrystallized from EtOH solution. This procedure gave 6.99 g (88%) of the ester (III).

The ethyl ester of N-(dimorpholidophosphoryl)-4-ACHC-DL-phenylalanine (XI) was synthesized in a similar manner. The ethyl esters of N-(dimorpholidothiophosphoryl)-trans-4-ACHC-DL-phenylalanine (IV) and N-

(dimorpholidothiophosphoryl)-cis-4-ACHC-DL-phenylalanine (XII) were prepared from N-(dichlorothiophosphoryl)-trans- and cis-4-ACHC-DL-phenylalanine by procedures similar to those used in the synthesis of (III); (IV) was recrystallized from EtOH and (XI)-(XII) from a 1 : 1 AcOEt–EtOH mixture.

Na Salt of N-(Tetramethyldiamidophosphoryl)-trans-4-ACHC-DL-phenylalanine (V). To a solution containing 2.26 g of ester (I) dissolved in 25 ml of CH_3OH there was added 4.16 ml of 1.2 N CH_3ONa (methanol) and 0.1 ml of H_2O, and the resulting mixture allowed to stand for 4 days at ~20°C. The insoluble residue which had formed at the end of this time was then filtered off and the solvent vaporized in vacuum. The residue was dried by azeotropic distillation of water and benzene, and then triturated with a 1 : 1 mixture of anhydrous ether and acetone. This procedure gave 2.06 g (89%) of the Na salt of (V).

The Na salts of (VI)-(VIII) and (XIII)-(XV) were prepared in a similar manner.

CONCLUSIONS

The ethyl esters and Na salts of N-(tetramethyldiamido(thio)phosphoryl)- and N-(dimorpholido(thio)phosphoryl)-cis- and trans-4-ACHC-DL-phenylalanine have been synthesized.

LITERATURE CITED

1. K. I. Karpavichyus (Karpavicius), L. A. Patotskene, and I. L. Knunyants, Izv. Akad. Nauk SSSR, Ser. Khim., 913 (1978).
2. K. I. Karpavichyus (Karpavicius), A. M. Yuodvirshas, N. F. Zakharova, A. I. Palaima, and A. P. Puzerauskas, The Search for and Study of Antitumorigenic, Antiphlogistic, and Mutagenic Substances [in Russian], Inst. Biokhim. Akad. Nauk LitSSR (1977), p. 161.
3. M. Freifelder and G. R. Stone, J. Org. Chem., 27, 3568 (1962).
4. A. I. Palaima, R. A. Poshkene, K. I. Karpavichyus (Karpavicius), O. V. Kil'disheva, and I. L. Knunyants, Izv. Akad. Nauk SSSR, Ser. Khim., 195 (1977).

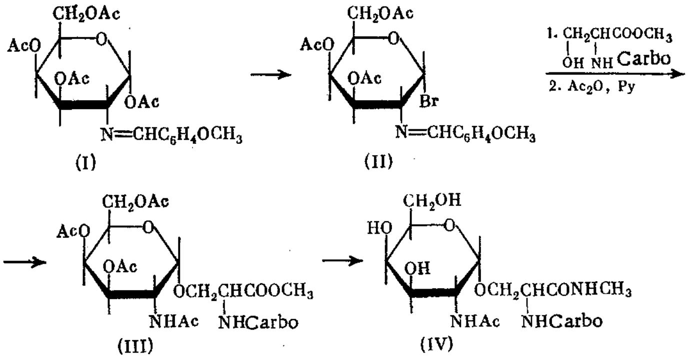
SYNTHESIS OF THE METHYLAMIDE OF O-[2-ACETAMIDO-2-DESOXY-α-D-GALACTOPYRANOSYL]-N-CARBOBENZOXY-L-SERINE

N. K. Kochetkov, V. A. Derevitskaya,
and O. S. Novikova

UDC 542.951.1:547.455

An N-acetyl-D-galactosamine residue joined to either serine or threonine by an α-glucoside bond is found in the O-glucoside carbon–peptide bond center of many glucoproteins [1, 2]. Study of the behavior of glucopeptides containing a natural carbon–peptide bond should contribute to an understanding of various aspects of the selective cleavage of bonds of this type.

We have accordingly carried out the synthesis of the methylamide of O-[2-acetamido-2-desoxy-α-D-galactopyranosyl]-N-carbobenzoxy-L-serine (IV):



N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 2, pp. 390-393, February, 1980. Original article submitted December 7, 1978.

0568-5230/80/2902-0302$07.50