A
THESIS
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SYNTHESIS OF SOME CHLOROPHENOXY ACETYL AMINO ACID AND PEPTIDE DERIVATIVES WITH POSSIBLE ANTIMICROBIAL ACTIVITY

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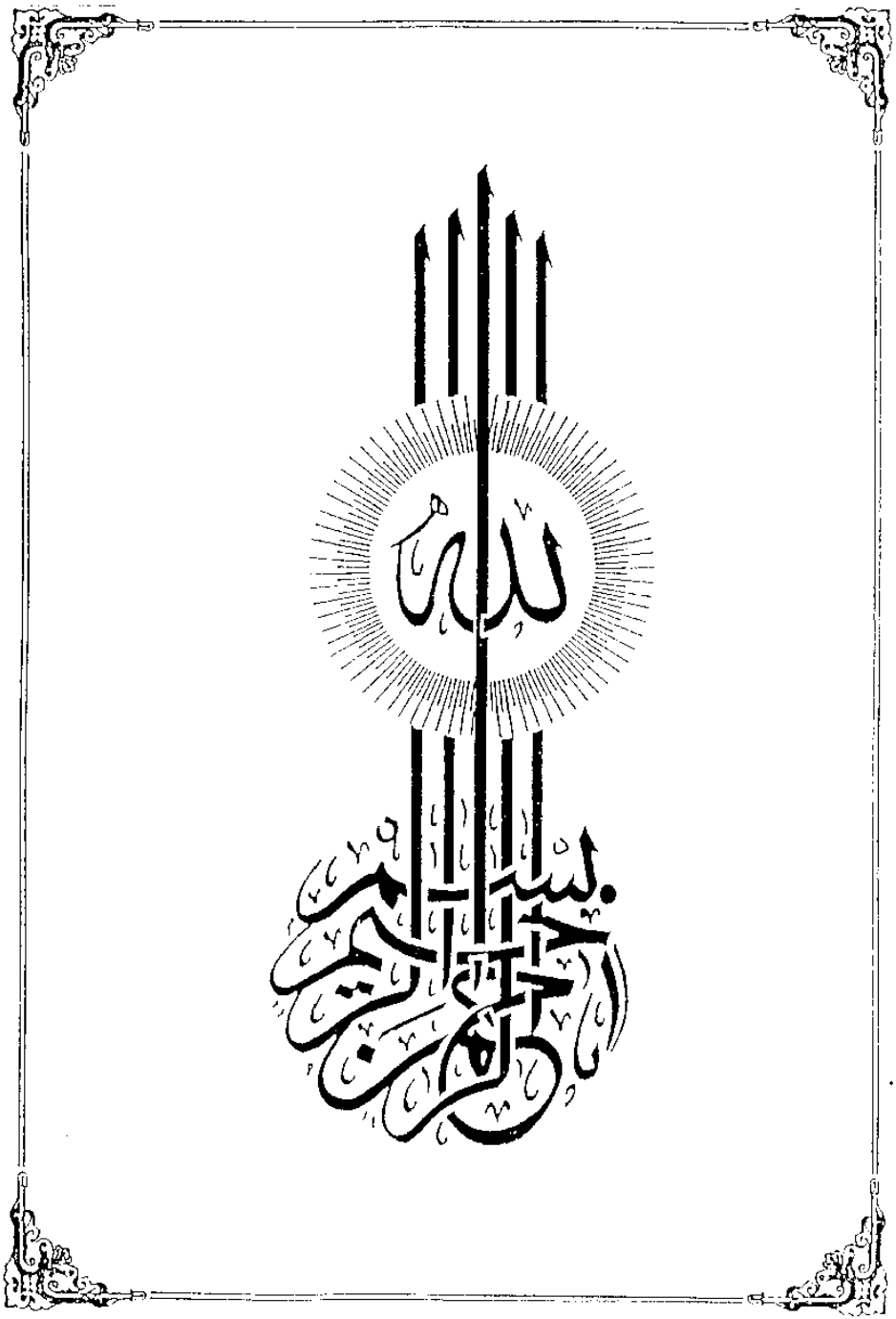

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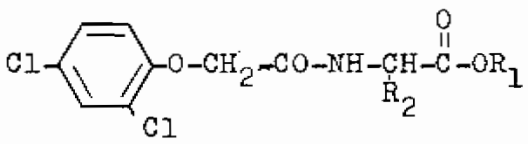
SUMMARY

SUMMARY OF THE ORIGINAL WORK

In search for new antimicrobial compounds with special reference to antitubercular agents, rationalized N-2,4-dichlorophenoxy acetyl amino acid and peptide derivatives including free acids (Ia-k), esters (IIa-k), hydrazides (IIIa-k) hydrazones (LVa-j), dipeptide ethyl esters (Va-g) dipeptidehydrazides (VIa-g) and dipeptide hydrazones (VIIa-g) have been synthesized.

The synthesized amino acid and peptide derivatives are presented in Tables (A) and (B), respectively.

Table (A)



Class	Comp. No.	R_1	R_2	Amino acid residue
I	Ia	OH	H	(Gly)
	b		CH_3	(L-Ala)
	c		$CH_2CH(CH_3)_2$	(L-Leu)
	d		$(CH_2)_2S-CH_3$	(DL-Met)
	e		$CH(CH_3)_2$	(DL-Val)
	f		$CH(CH_3)_2$	(D-Val)
	g		$CH(CH_3)_2$	(L-Val)
	h		$(CH_2)_2-S-CH_3$	(L-Met)
	i		$CH_2-C_6H_5$	(DL-Phe)
	j		$CH_2-C_6H_5$	(L-Phe)
	k		$CH_2-C_6H_5$	(D-Phe)

(Cont.)

Table (A) cont.

Class	Comp. No.	R_1	R_2	Amino acid residue
II	IIa	OEt	H	(Gly)
	b		CH_3	(L-Ala)
	c		$CH_2-C_6H_5$	(DL-Phe)
	d		$CH_2-C_6H_5$	(L-Phe)
	e		$CH_2-C_6H_5$	(D-Phe)
	f		$(CH_2)_2-S-CH_3$	(DL-Met)
	g		$(CH_2)_2-S-CH_3$	(L-Met)
	h		$CH_2-CH-(CH_3)_2$	(L-Leu)
	i		$CH(CH_3)_2$	(DL-Val)
	j		$CH(CH_3)_2$	(L-Val)
	k		$CH(CH_3)_2$	(D-Val)
	l		$(CH_2)_2NHCOOCH_2Ph$	L-Dab(Z)
III	IIIa	$NHNH_2$	H	(Gly)
	b		CH_3	(L-Ala)
	c		$CH_2-C_6H_5$	(DL-Phe)
	d		$CH_2-C_6H_5$	(L-Phe)
	e		$CH_2-C_6H_5$	(D-Phe)
	f		$(CH_2)_2-S-CH_3$	(DL-Met)
	g		$(CH_2)_2-S-CH_3$	(L-Met)
	h		$CH_2-CH(CH_3)_2$	(L-Leu)
	i		$CH(CH_3)_2$	(DL-Val)
	j		$CH(CH_3)_2$	(L-Val)
	k		$CH(CH_3)_2$	(D-Val)
	l		$(CH_2)_2NHCOOCH$ Ph	L-Lab(Z)
IV	IVa	$NH-N=R_3^*$	H	(Gly)
	b		CH_3	(L-Ala)
	c		$CH_2-C_6H_5$	(DL-Phe)
	d		$CH_2-C_6H_5$	(L-Phe)
	e		$(CH_2)_2-S-CH_3$	(DL-Met)
	f		$(CH_2)_2-S-CH_3$	(L-Met)
	g		$CH_2\ CH(CH_3)_2$	(L-Leu)

Table (A) cont.

Class	Comp. No.	R_1	R_2	Amino acid residue
IV	IVh	$NH-N=R_3$ *	$CH(CH_3)_2$	(DL-Val)
	i		$CH(CH_3)_2$	(L-Val)
	j		$CH(CH_3)_2$	(D-Val)
	k		$(CH_2)_2NHCOOCH_2Ph$	L-Dab(Z)

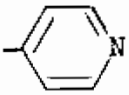
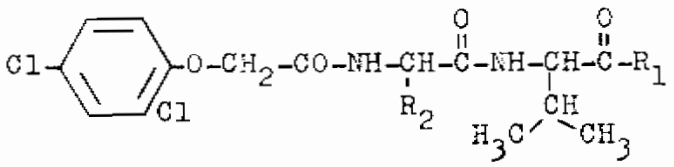
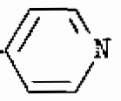
* R_3 = CH– 

Table (B)



Class	Comp. No.	R_1	R_2	Amino acid residue
V	V a	OEt	H	(Gly)
	b		CH_3	(L-Ala)
	c		$CH_2-CH(CH_3)_2$	(DL-Leu)
	d		$(CH_2)_2S-CH_3$	(DL-Met)
	e		$CH-(CH_3)_2$	(DL-Val)
	f		$CH(CH_3)_2$	(L-Val)
	g		$CH(CH_3)_2$	(D-Val)
VI	VI a	$NHNH_2$	H	(Gly)
	b		CH_3	(L-Ala)
	c		$CH_2-CH(CH_3)_2$	(L-Leu)
	d		$(CH_2)_2-S-CH_3$	(DL-Met)
	e		$CH(CH_3)_2$	(DL-Val)
	f		$CH(CH_3)_2$	(L-Val)
	g		$CH(CH_3)_2$	(D-Val)
VII	VII a	$NH-N=R_3^*$	H	(Gly)
	b		CH_3	(L-Ala)
	c		$CH_2-CH(CH_3)_2$	(L-Leu)
	d		$(CH_2)_2-S-CH_3$	(DL-Met)
	e		$CH(CH_3)_2$	(DL-Val)
	f		$CH(CH_3)_2$	(L-Val)
	g		$CH(CH_3)_2$	(D-Val)

* R_3 = CH- 

N-2,4-dichlorophenoxy acetyl amino acids (Ia-k, Table 20) were prepared by one of the two methods - acid chloride method or alkaline hydrolysis of the corresponding esters. DCPA was reacted through its acid chloride with the free amino acid in presence of aq. NaOH at pH 8-10 and low temperature to give the corresponding amino acid derivatives I(a-g) in 45-81% yield. The rest of the synthesized amino acid derivatives I(h-k) have been obtained by the alkaline hydrolysis of the corresponding N-(2,4-dichlorophenoxy acetyl amino acid ethyl esters (table 21) in 40-75 % yield . Originally, it was planned to prepare these acids Ia-g by the direct alkaline hydrolysis of the corresponding esters. However, some difficulties were encountered during hydrolysis e.g. steric hindrence.

N-2,4-dichlorophenoxy acetyl amino acid esters (Table 21) have been synthesized II(a-l) by two different routes. The first method is the carbodiimide method in acetonitrile which was used for the synthesis of the majority of the required amino acid esters II(a-i, l).

Attempts to use CH_2Cl_2 as solvent medium, afforded different unidentifiable products. On the other hand, the rest ofthe required esters (IIj-k) have been obtained by the direct esterification of the corresponding DCPA-amino acids using thionyl chloride/EtOH in 33-40 % yield.

N-2,4-dichlorophenoxy acetyl aminoacid hydrazides (III a-l, Table 22) have been easily obtained, in good yield,

by the action of 20- fold excess of hydrazine hydrate on the corresponding esters II(a-l), in ethyl alcohol.

N-2,4-dichlorophenoxyacetyl amino acid hydrazone (IV a-k, Table 23) were prepared by condensation of the corresponding hydrazides (III a-d, f-l Table 22) with isonicotinaldehyde in refluxing ethanol in fair yields 55-91%. Isonicotinaldehyde was the carbonyl compound of choice since it bears structural resemblence to INH. In addition to the enhanced broad antimicrobial spectrumof many pyridine derivatives.

The synthesis of the N-(2,4-dichlorophenoxyacetyl)dipeptide ethyl esters (Va-g, Table 24) has been achieved by using the DCCI procedure from the corresponding N-2,4-dichlorophenoxy acetyl amino acids (Ia-g) and L-valine ethyl ester hydrochloride in acetonitrile and NEt_3.. This procedure afforded chromatographically homogeneos products in 31-92% yield.

The dipeptide hydrazide (VIa-g, Table 25) were readily obtained in a crystalline form by refluxing the corresponding dipeptide esters (Va-g) with an excess of hydrazine hydrate (80%) in ethanol.

The N-(2,4-dichlorophenoxy acetyl)dipeptide hydrazone (VIIa-g) were easily obtained by the condensation of equimolecular amounts of the corresponding hydrazides(VI. a-g) and isonicotinaldehyde. The products were obtained as

pure crystalline solids in 29-68% yield.

The purity of the synthesized compounds as well as the starting materials was checked by thin layer chromatography. The structures were confirmed by elemental analysis and in many cases by UV, IR and mass specrtoscopy. The 2,4-dichlorophenyl nucleus was located at λ_{max} 210 nm and 282 nm. The peptide bond exhibited its characteristic IR absorption bands at 1660-1620, 1550-1475 and 1380-1215 cm^{-1} (amid I, II and III bands, respectively). The study of the fragmentation patterns in the mass spectra of some compounds representing the different classes has revealed some interesting peaks attributed to rearrangement fragments.

The antitubercular activity of the synthesised compounds are still under investigation and will be published elsewhere.

NOMENCLATURE and ABBREVIATIONS

Unless otherwise stated , The used amino acids are amino acids of L-configuration.

Nomenclature and abbreviations generally follow the recommendations of the IUPAC- IUP commission on Biochemical Nomenclature (J. Biol. Chem. 247, 977, 1972). The following abbreviations are used.

PAB : p-amino benzoic acid

Gly : Glycine

Nic : Nicotinoyl

iso Nic.: isonicotinoyl

Met : Methionine

Pic : Picolinoyl

PAS : p-amino salicylic acid

INH : Isonicotinic acid hydrazide

-OEt : ethyl ester

-OMe : methyl ester

$-N_2H_3$: hydrazide

CPA : 4-chlorophenoxy acetyl

DCPA : 2,4-dichlorophenoxy acetyl

TCPA : 2,4,6-trichlorophenoxy acetyl

Dab(Z) : N^4 cabobenzoxy-L-2,4-diaminobutyric acid

EtOAc : Ethyl acetate

AcOH : Acetic acid