SYNTHESIS OF SOME SUBSTITUTED FURAN AMINO ACID DERIVATIVES

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SUMMARY

Some substituted furan amino acid derivatives were prepared from 5-bromo furoyl chloride and 5-nitrofuran acryloyl chloride.
Some of the prepared compounds were found to be highly active against gram negative bacteria.

Introduction

Some nitrofurans exhibit antimicrobial activity and have been used as chemotherapeutic agent (Ebenito, 1974, Miwa and Reckendorf, 1967). Also a number of furan amino acid derivatives were reported and found to he biologically active (Peterson and Jelleum, 1972, Hiroshi and Kyushu, 1950, El-Naggar and Abd-El-Rahman, 1976).

The importance of furan-2-amino acid derivatives from the point of view of pharmaceutical chemistry attracted the authors to synthesize several substituted furan amino acid derivatives which may enhance the activity of these compounds or verify their biological action.

In the present work, the synthesis of some 5-bromo-2- furoylamino acids, 5-bromo-2-furoyl amino acid methyl esters and 5-nitrofuran-2-acryloylamino acid methyl esters and 5-nitrofuran-2-acryloylamino acid methyl esters were described and their antimicrobial activities were screened.

Experimental

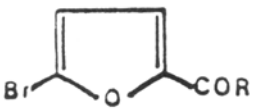
All melting points are uncorrected and done by using Gallenkamp melting point apparatus. The purity of the products were checked by TLC. The solvent system is Toluene, Ethyl acetate, Acetic Acid (12:4:0.5v/v) and chlorosulphonic acid in acetic acid used as a spraying agent. IR spectra were taken by Perkin-Elmer 580-B Spectrophotometer. For the electrophoretic mobility of the prepared compounds pyridine; acetate buffer solution system was used. The specific rotations were done by using Polarimeter Model 241 MC Perkin-Elmer instrument. The elemental analysis were done by using Perkin-Elmer 240-B elementer analyser.

15-Bromo-2-Furoyl Chloride (Compound I)

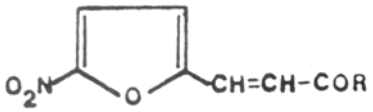
This compound was prepared according to the procedure described by Raiford (Raiford and Huey, 1941) and 5-nitrofuran-2-acryloyl chloride (Compound II) was prepared by the proecedure described by venters (Venters, *et al.,* 1962) and Tadashi (Tadashi, 1954).

2. General Procedure for the Synthesis of 5-Bromo-2-Furoylamino Acids (Compound III-V)

0.05 mol of amino acid was dissolved in 100 ml of IN KOH solution. The mixture was cooled to 7°C and 0.51 mol of 5-bromo-2-furoyl chloride in 100 ml benzene was added dropwise in the course of 1 hr while stirring. The reaction mixture was strirred for 3.5 hrs. and unreacted material filtered. The solution was cooled to 0°C and acidified with 2N HCI to pH 5. The crude product was filtered and recrystallised from appropriate solvent (Table-I).



Type-A
I



Type-B
II

TABLE-1

Comp.No.	R	Yield %	mp °C	Rf	Crystallisation Solvent
TYPE - A					
III	L-Val	71	281-283	0.81	DMF
IV	L-Leu	83	157-159	0.76	DMF
V	DL-nor-Leu	75	160-162	0.84	DMF
VI	Gly-OMe	65	59-61	0.63	Petro.ether
VII	B-Ala-OMe	65	143-145	0.70	Petro.ether
VIII	DL-Ser-OMe	76	105-107	0.86	EtOH-Water
IX	L-Tyr-OMe	63	133-135	0.69	EtOH-Water
X	L-Ser-OMe	71	101-103	0.73	EtOH-Water

Table continued

TYPE - B

XI	Gly-OMe	60	188-190	0.42	EtOH-Petr.-Ether
XII	L-Ala-OMe	50	179-181	0.75	Benz.Petr.-Ether
XIII	B-Ala-OMe	61	184-186	0.71	Benz.-Petr.-Ether.
XIV	DL-nor-Leu-OMe	66	174-176	0.54	Benz.-Petr.-Ether.
XV	DL-Phe-OMe	55	267-269	0.76	Benz.-Petr.-Ether
XVI	L-Ser-OMe	58	114-116	0.68	EtOH-Water
XVII	L-Tyr-OMe	46	155-156	0.60	Carbon tetra-chlororide
XVIII	L--Trp-OMe	50	110-112	0.53	Benz.-Petr.-Ether.

Table II- A

The Elementel Analysis of the Compounds Type -A

Comp.No	$[\alpha]^{20}_D$	Molecular Form.	Elementer Analysis Calcd./Found
Type A			
III	+49.7(c=0.4DMF)	$C_{10}H_{12}NO_4Br$	C:41.40,H:4.16,N:4.82 C:41.34,H:4.07,N:4.89
IV	+51.4(c=0.6DMF)	$C_{11}H_{14}NO_4Br$	C:43.44,H:4.63,N:4.61 C:43.51,H:4.57,N:4.72
V	+47.3(c=0.6DMF)	$C_{11}H_{14}NO_4Br$	C:43.44,H:4.63,N:4.61 C:43.38,H:4.70,N:4.68
VI	+17.3(c=0.5DMF)	$C_8H_8NO_4Br$	C:36.66,H:3.07,N:5.34 C:36.54,H:2.98,N:5.44
VII	+19.2(c=0.5DMF)	$C_9H_{10}NO_4Br$	C:39.15,H:3.65,N:5.07 C:39.02,H:3.73,N:5.00
VIII	+21.1(c=0.6DMF)	$C_9H_{10}NO_5Br$	C:37.00,H:3.45,N:4.79 C:37.09,H:3.38,N:4.82
IX	+47.8(c=0.6DMF)	$C_{15}H_{14}NO_5Br$	C:48.93,H:3.83,N:3.80 C:48.85,H:3.89,N:3.90
X	+105.43(c=0.4DMF)	$C_9H_{10}NO_5Br$	C:37.00,H:3.45,N:4.79 C:37.10,H:3.53,N:4.84

Table II-B

The Elementel Analysis of the Compounds Type-B

Comp.No	$[\alpha]^{20}_D$	Molecular Form.	Elementer Analysis Calcd./Found
Type-B			
XI	+60(c=0.5DMF)	$C_{10}H_{10}N_2O_6$	C:47.25,H:3.96,N:11.02 C:47.13,H:3.88,N:10.99
XII	+72.1(c=0.5DMF)	$C_{11}H_{12}N_2O_6$	C:49.25,H:4.50,N:10.45 C:49.16,H:4.48,N;10.54
XIII	+63(c=0.6DMF)	$C_{11}H_{12}N_2O_6$	C:49.25,H:4.50,N:10.45 C:49.32,H;4.57,NIL10.58
XIV	+13.2(c=0.9MDF)	$C_{14}H_{18}N_2O_6$	C;54.18,H:5.84,N:9.03 C:54.25,H:5.73,N:9.17
XV	+16.3(c=0.7DMF)	$C_{17}H_{16}N_2O_6$	C:59.30,H:4.69,N:8.13 C:59.21,H:4.59,N:8.20
XVI	+17.7(c=0.6DMF)	$C_{11}H_{12}N_2O_6$	C:46.8, H:4.25,N:9.86 C:46.57,H:4.23,N:9.96
XVII	+33.2(c=0.6DMF)	$C_{17}H_{16}N_2O_6$	C:59.30,H:4.68,N:7.78 C:59.40,H:4.57,N:7.97
XVIII	+74.8(c=0.5DMF)	$C_{19}H_{17}N_3O_6$	C:59.52,H:4.46,N:10.96 C;59.43,H:4.43,N:10.98

3. General procedure for the preparation of Amino Acid Methyl Ester Hydrochlorides

The esters were prepared by the method described by Brenner and Huber (Brenner and Huber, 1953).

0.01 mol of amino acid was dissolved in 0.5 mol of MeOH and cooled to -10°C. Onto this solution 0.011 mol of Socl2 was added dropwise then the temperature al-lowed to raise to 40°C and held at this point for 2 hrs. Excess of MeOH was evaporated, and the methyl esters were obtained with 70-80% yield.

4. General procedure for the Synthesis of 5-Bromn-2-Furoyl Amino Acid Methyl Esters (Compound VI-X)

0,04 mol of Compound I was dissolved in 60 ml peroxide free dioxane. Onto this solution 0.05 mol amino acid methyl ester hydrochloride in 100 nil dioxane containing 10 ml EI3N was added. The reaction mixture was stirred at nom temperature followed by

relluxing until completion of the reaction mixture. Et_3N, HCl was littered and 250 ml benzene: ether (1:1) was added. Then the reaction mixture was washed, dried over sodium sulphate evaporated and recrystallised front appropriate solvent (Table 1).

5. General Method for the synthesis of 5Nitrofuran- 2Acryloyl Amino Acid Methyl Esters (Compound XI-XVIII).

0.029 mol of amino acid methyl ester HCl was dissolved in 120 ml of peroxide free dioxane containing 12 ml Et_3N. Onto this solution 0.025 mot of Compound II in 150 ml dioxane was added. The reaction mixture was stirred at room temperature followed by reflux till completion which is monitored by TLC. The remaining procedure was similar as described above.

6. The Antimicrobial Activity

The screening of the antibacterial activity was performed by using disk diffusion plate method (Vincent and Vincent, 1944). The data's are given in Table-III.

Table-III

Activity (A) and Minimum Inhibitory Concentration (MIC) calculated as pg/ml.

Comp. No.	B.subtitis (lcc strain) A.MIC	B.mycoides (USSR) A.MIC	B.cereus (NRR B-503) A.MIC	E.coli (NRR-B 510) A.MIC	S.typhosa (NRR-B-573) A.MIC
XI	... 6	... 6	.. 12.5	... 6	. 50
XII	.. 12.5	.. 12.5			-
XIII	.. 12.5	... 6	. 50		. 50
XIV	.. 12.5	... 6	.. 12.5	. 50	. 50
XV	. 50				
XVI	.. 12.5	.. 12.5	.. 2.5	. 50	-
XVII	.. 12.5	.. 12.5	.. 12.5		-
XVIII	.. 12.5	.. 12.5	. 50		

Results and Discussion

When 5-bromo-2-furoyl chloride (Compound I) was reacted with appropriate amino acid (1:1.1 mol) in benzene potassium hydroxide medium, 5-bromo-2-furoyl amino acids were obtained (Compound 111-V). Most of the products were obtained in crystalline form in 71-83% yield. For the preparation of 5- bromo-2-furoyl amino acid methyl esters (Compound VI-X). Compound I was treated with amino acid methyl ester HCl's (1:1.2 mol) in medium of peroxide free dioxane-Et_3N. The methylesters of amino acids were prepared by the interaction of amino acid, MeOH and Socla. The synthesis of 5-bromo-2-furoyl-GlyOme (Compound VI) was successively performed and the product easily isolated, purified and recrystallized. The reaction of Compound I with B-Ala, Ser and Tyr methyl esters were carried out under the same conditions as used for the preparation of Compound VI and the time required for completion of the reaction is 30 min. -4 hrs which was monitored by TLC. Most of the products (Compounds VI-X) were obtained in crystalline form with the yield of 63-71% and they all gave chromatographically homogenous spots.

Synthesis of 5-nitrofuran-2-acryloyl amino acid esters (Compound XI-XVIII) were carried out by the reaction of 5-nitrofuran-2-acryloyl chloride (Compound-II) with appropriate amino acid methyl esters HCl in peroxide free dioxane in the presence of Et3N. Compounds XI-XVIII were prepared using similar conditions as described for the preparation of Compounds VI-X. The products (Compound XIXVIII) were easily purified and recrystallized. The structures of all compounds, III-XVIII, were well supported by their characteristic IR spectra.

All 5-nitrofuran-2-acryloyl amino acid methyl esters (Compound XI-XVIII) were found to be highly active against Bacillus subtilis, Bacillus mycoides, Bacillus cercus, Escherichia coli, Salmonella typhosa and inactive against Penicillum chrysogenum. The remaining 5-bromo-2-furoyl amino acid derivatives (Compound III-X) were inactive against all microorganisms tested.

The high biological activity of compounds XI-XVIII may be attributed to the presence of three active centers; the 5-nitro group, furan acrylic acid residue and the amino acid moiety incorporated in the molecule.

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