SYNTHESIS AND PROPERTIES OF SOME DERIVATIVES OF THIAZOLECARBOXYLIC AMINO ACIDS

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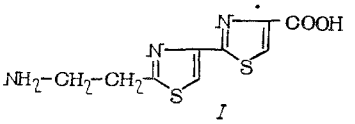
The recently discovered and investigated antibiotic bleomycin [1] is a glycopeptide containing four previously unknown amino acids. Among them are 2'-(β-aminoethyl)-2,4'-bithiazole-4-carboxylic acid (I), whose synthesis has recently beem achieved [2].

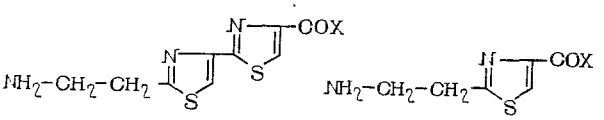
Here we describe the synthesis of compounds III-V, which result from the transformation of the carboxylic group in acid I. A study was made of the extent to which these compounds suppressed the synthesis of nucleic acids in vitro; a culture of strain NK/Ly of lympholeukosis was used. For comparison we also synthesized derivatives (IIIa-Va) of a sample Ia, namely 2-(β-aminoethyl)thiazole-4-carboxylic acid (II), because it is known that (aminoalkyl)thiazolecarboxylic acids are included in the structure of certain antibiotics [3]. Deacylation of the phthalyl derivatives by the amino group was effected by the method described in [4].

The properties of the synthesized compounds are given in Table 1.

It can be seen from Table 1 that the compounds listed are able to inhibit the synthesis of nucleic acids in vitro. Comparison of the derivatives of bi- and monothiazolecarboxylic acids shows that with the exception of the amino acids themselves their derivatives display approximately the same inhibitory influence, and that the most active is compound I. We may conclude that on the whole the synthetic derivatives of I are worthy of study for their biological activity.



I

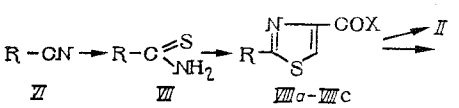


III-V

III, IIIa: X = OC_2H_5
IV, IVa: X = NH_2
V, Va: X = NH–NH_2

IIIa-Va

The compounds were synthesized as follows:



VI VII VIIIa-IIIc II

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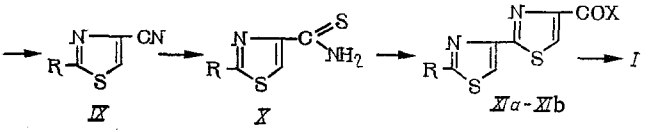
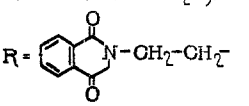


for compounds XI and XI: a) X=OH, b) X=OC_2H_5, c) $X=NH_2$

for all compounds: 

EXPERIMENTAL METHOD

β-Phthalylaminopropionic Thioamide (VII). Hydrogen sulfide was passed through a solution of 15 g VI in 60 ml dimethylformamide and 15 ml diethylamine for 4 h, and left to stand overnight. The mixture was then poured into water, and the residue which settled out was filtered off, and washed with water. Yield 85%.

Ethyl 2-(β-Phthalylaminoethyl)thiazole-4-carboxylate (VIIIb). Prepared by heating 0.01 moles VII and 0.02 moles of ethyl bromopyruvate in absolute alcohol on a water bath for 2 h. Crystals settled out on standing; they were filtered off and washed with absolute alcohol.

2-(β-Phthalylaminoethyl)thiazole-4-carboxylic Acid (VIIIa). Prepared by hydrolysis of 0.001 moles VIIIb in 5 ml glacial acetic acid and 2 ml of concentrated hydrochloric acid by boiling for 2 h. After it had been cooled, the mixture was poured into water; precipitate was separated, and washed with water.

2-(β-Phthalylaminoethyl)thiazole-4-carboxamide (VIIIc). A suspension of 0.01 moles VIIIb in 10 ml of a 25% aqueous ammoniacal solution was stirred for 24 h. The precipitate was filtered off, and washed with water.

2-(β-Aminoethyl)thiazole-4-carboxylic Acid Hydrochloride (II). A mixture of 0.002 moles VIIIa in 20 ml ethyl alcohol and 6.6 ml (0.04 moles) 3% alcoholic hydrazine hydrate was boiled for 1 h. The solvent was evaporated, 20 ml more of alcohol was added, and the pH brought to 4.0-5.0 with hydrochloric acid. The phthalylhydrazide which separated out was removed, the filtrate was evaporated almost to dryness, filtered, and acetate was added to the filtrate drop by drop. The precipitate was removed by filtration.

The hydrochlorides of IIIa and IVa were obtained in the same way as II, from VIIIb and VIIIc.

Sodium 2-(β-Phthalylaminoethyl)thiazole-4-carboxylic Acid (IX). Obtained by boiling VIIIc with phosphoryl chloride for 2 h. The excess phosphoryl chloride was evaporated off, the remaining mixture was poured into ice, and the oily liquid which separated was allowed to crystallize. The crystals were removed, and washed with water.

2-(β-Phthalylaminoethyl)thiazole-4-thiocarboxyamide (X). Preparation was similar to that of VII. The time for which hydrogen sulfide was passed through the solution was 2 h.

Compounds XIa-XIc. Preparation similar to that of VIIIa-VIIIc.

Ethyl 2'-(β-Aminoethyl)-2,4'-bithiazole-4-carboxylate Hydrochloride (III). 0.02 moles XIb was heated with 20 ml of ethyl alcohol and 6.6 ml (0.04 moles) of 3% alcoholic hydrazine hydrate was added. The mass was then left to stand at room temperature for 24 h. Hydrochloric acid was added to bring the pH to 4.0-5.0; the mixture was then refrigerated for 2 h, and the precipitate which settled out was filtered off. The filtrate was reduced to half the original volume by evaporation, and refrigerated. A precipitate of III hydrochloride was formed, and was filtered off.

Hydrochlorides of I and IV. These substances were prepared similarly.

TABLE 1. Derivatives of 2-(β-Aminoethylthiazole) and -bithiazolecarboxylic Acids

Compound	Yield, %	mp (in deg)*	Found, %					Empirical formula	Calc., %					Concn. inhibiting synthesis of nucleic acids (μg/ml)
			C	H	Cl	N	S		C	H	Cl	N	S	
I	60	268	—	—	—	—	—	—	—	—	—	—	—	0,1
II	50	236	—	—	—	—	—	—	—	—	—	—	—	1
III	62,5	237	41,30	4,68	11,10	13,12	20,00	$C_{11}H_{13}N_3O_2S_2 \cdot HCl$	41,44	4,42	10,97	12,87	19,52	20
IV	60	215	37,20	3,78	12,20	19,30	—	$C_9H_{10}N_4OS_2 \cdot HCl$	37,61	4,31	12,70	19,35	—	50
V	90	243—245	35,40	3,50	11,60	23,00	21,00	$C_9H_{11}N_5OS_2 \cdot HCl$	35,00	3,50	11,31	23,25	20,88	75
IIIa	50	165	40,50	5,50	15,00	11,82	13,50	$C_8H_{12}N_2O_2S \cdot HCl$	40,53	5,40	15,30	11,96	13,56	20
IVa	60	234	—	—	17,10	20,15	15,45	$C_6H_9N_3OS \cdot HCl$	—	—	16,91	20,08	15,75	50
Va	90	193—195	—	—	15,90	25,20	14,40	$C_6H_{10}N_4OS \cdot HCl$	—	—	16,00	25,38	13,97	100
VIIIa	95	210	—	—	—	9,30	10,60	$C_{14}H_{10}N_2O_4S$	—	—	—	9,41	10,25	—
VIIIb	75	98—99	—	—	—	8,50	9,70	$C_{16}H_{14}N_2O_4S$	—	—	—	8,41	9,60	—
VIIIc	235	70	$C_{14}H_{11}N_3O_3S$	—	—	—	14,00	10,65	—	—	—	14,27	10,42	—
IX	148—150	95	$C_{14}H_9N_3O_2S$	59,50	3,18	—	14,95	11,30	50,56	3,31	—	15,20	11,83	—
X	220—222	96,5	$C_{14}H_{11}N_3O_2S_2$	—	—	—	13,25	20,19	—	—	—	13,31	20,18	—
XIa	222	70	$C_{17}H_{11}N_3O_4S_2$	—	—	—	10,90	16,60	—	—	—	11,08	16,26	—
XIb	150	98	$C_{19}H_{15}N_3O_4S_2$	—	—	—	10,20	15,50	—	—	—	10,40	15,72	—
XIc	251	100	$C_{17}H_{12}N_4O_3S_2$	—	—	—	14,60	16,70	—	—	—	15,23	16,99	—

*Compound III was recrystallized from isopropyl alcohol, IV and VIIIb from absolute alcohol, V and Va from methyl alcohol, Ia from ethyl alcohol and ether, IVa, VIIIc, IX, X, XIa, and XIb from ethyl alcohol, VIIIa and XIc from water.

2-(β-Aminoethyl)thiazole-4-carboxylhydrazide and 2'-(β-Aminoethyl)-2,4'-bithiazole-4-carboxylhydrazide (V, Va). Prepared by heating the corresponding ethyl esters with hydrazine hydrate in alcoholic solution and then evaporating off the solvent.

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