# SYNTHESIS AND BIOLOGICAL ACTIVITY OF CYSTEINE AND THIAZAOLIDINE-4-CARBOXYLIC ACID DERIVATIVES

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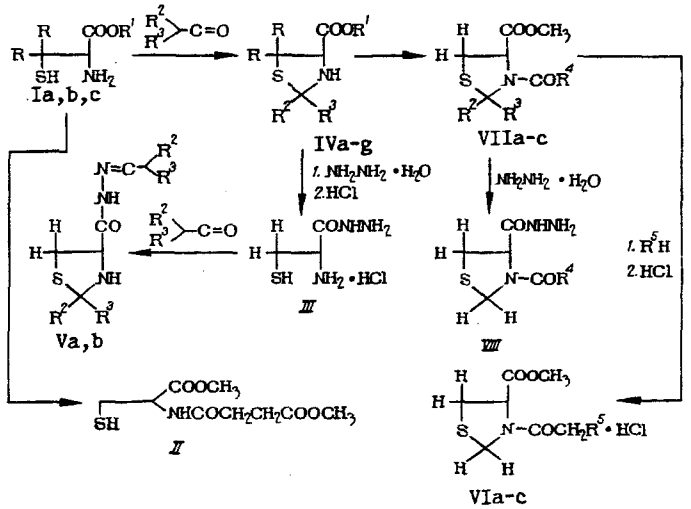
A number of compounds containing mercapto and carboxylic groups together with some form of modified amino group (amide or amidine moieties [4]) are known to be capable of inhibiting angiotensin-converting enzyme (kininase II, ACE) and are of interest as potential antihypertensive agents [11]. Moreover, compounds of this type may exert an effect on the activity of the endogenous antinociceptive system, since kininase II belongs to a group of enzymes involved in the inactivation of endogenous opioid peptides [10, 27].

It has been established that cysteine (Ia) and penicillamine (Ib) are kininase II inhibitors and that modifying the structures of these amino acids may be useful in obtaining new antihypertensive drugs [4, 8, 9].

The aim of this study was to examine the biological activity of derivatives of cysteine and penicillamine (Ic, II, III), including cysteine hydrazide (III)*, and chiefly cyclic derivatives of these amino acids – substituted thiazolidine-4-carboxylic acids and their esters. These cyclic compounds are chosen for study because they are more hydrophobic than the parent amino acids and can more easily pass through lipid barriers. On the other hand, it is known that the thiazolidine ring of these compounds may be more or less easily cleaved, depending on the substituents, regenerating the corresponding substituted amino acid.



Ia: R=R¹=H; Ib: R=Me, R¹=H; Ic: R=H, R¹=Me; IVa: R=R¹=R²=R³=H; IVb: R=R²==R³=H; R¹=Me; IVc. R=R¹=H; R²=R³=Me; IVd. R=H, R¹=R²=R³=Me; IVe R=Me, R¹=R²=R³=H; IVf: R=R¹=R³=H, R²=Rh; IVg: R=Me, R¹=R³=H; R²=Ph; Va. R²=R³=Me; Vb: R²=H, R³=Ph; VIa R⁵=N(CH₂)₅; VIb: R⁵==N(CH₂CH₂)₂NMe; VIc R⁵=N(CH₂CH₂)₂O; VIIa: R²=R³=H, R⁴=Me; VIIb: R²=R³=H, R⁴==CH₂Cl; VIIc: R²=R³=Me; R⁴=Ph.

The ester of N-(β-methoxycarbonylpropionyl)cysteine (II) was obtained by reaction of cysteine (Ia) with the monomethyl ester of succinic acid in the presence of dicyclohexylcarbodiimide.

The structure of this compound as an N-acyl (and not an S-acyl) derivative is clearly established by its $^1$H-NMR spectra. The multiplicity and relative intensity of signals corresponding to CH- and NH-group protons confirms structure II. Indeed, the NH proton spectral signal was observed in the form of a doublet at 6.74 ppm ($^3J_{NH,CN}$ 7.6 Hz) due to the spin-spin interaction with the CH proton, which appears at 4.87 ppm (quartet). The intensity of both signals is 1 relative unit each. If the SH group took part in the reaction, the inten-

*We have already discussed the possible effect of acid hydrazides on the activity of kininase II inhibitors such as captopril and amidinomercaptoacids [3, 4].

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TABLE 1. Effect of Cysteine and Thiazolidine Derivatives on AP in Rats with Renovascualr Hypertension (RVH) and Spontaneously Hypertensive Rats (SHR), on Pressor Action of A-I, on Depressor Action of BK, and on ACE Activity in Vitro

| Compound | Antihypertensive activity 1 h after administration (dose 10% $LD_{50}$, p/o) | | Effect on A-I pressor action (dose 1 mg/kg, iv) | Effect on BK depressor action (dose 1 mg/kg, iv) | ACE inhibition (% inhibition at a a concentration of $10^{-4}$ mole) |
|---|---|---|---|---|---|
| | RVH | SHR | | | |
| Ic | −15 | −22 | −16 | +40* | $3{,}5 \cdot 10^{-5}$** |
| III | −16 | −19 | −7 | +25 | $1 \cdot 10^{-4}$** |
| II | 0 | 0 | 0 | 0 | |
| IVa | 0 | 0 | 0 | −80* | |
| IVb | 0 | 0 | 0 | 0 | |
| VIIa | −15 | −13 | 0 | +30 | 31 |
| VIII | 0 | 0 | 0 | −40* | |
| VIIb | 0 | 0 | 0 | 0 | |
| VIa | 0 | 0 | 0 | 0 | |
| VIb | 0 | +19 | 0 | −70 | |
| VIc | 0 | 0 | 0 | −20 | |
| IVc | −10 | −17 | −10 | +10 | 15 |
| IVd | −29* | −26* | −35* | +90* | $4{,}0 \cdot 10^{-5}$ |
| Vd | 0 | 0 | 0 | 0 | |
| VIIc | 0 | 0 | 0 | −40* | |
| IVe | 0 | 0 | 0 | 0 | |
| IVf | −40* | −28* | −30* | +100* | $3{,}2 \cdot 10^{-5}$ |
| Vb | 0 | 0 | 0 | 0 | |
| IVg | 0 | 0 | 0 | 0 | |
| Ia | −19* | −22* | −12 | +80* | $1 \cdot 10^{-4}$ |
| Captopril (25 mg/kg) | −38* | −42* | −100* | +160* | $1 \cdot 10^{-9}$ |

*Difference from control significant at $P < 0.05$.
**Concentration inhibiting ACE activity by 50%.
Note. p/o denotes peroral administration of compound, iv denotes intravenous adminsitration.

sity of the $NH_2$ signal would be twofold higher, and the multiplet CH signal would also be different, since it would be split by two protons of an $NH_2$ group instead of one. The synthesis of compounds III, IVa-f, Va, b, VIIa, and VIII have been described in the literature [1, 2, 5, 14, 15, 19-22, 25, 26]. It should be noted that when compound Va was synthesized under the conditions described in [2], the reaction did not proceed to completion and in addition to the desired product Va in the reaction mixture, a compound (or compounds) remained containing one acetonyl moiety ($M^{+\cdot}$ 175)). Only a significant increase in condensation time allowed Va to be obtained in pure form.

The synthesis of N-acyl derivatives (VIa-c) was achieved by reaction of the N-chloroacetyl derivative (VIIb) with secondary amines.

## EXPERIMENTAL (CHEMICAL)

Mass spectra were obtained on an MAT-112 Varian spectrometer, injecting the sample directly into the ion source. The temp. of the ionization chamber was 180°C. The energy of the ionizing electrodes was 70 eV. The $^1$H-NMR spectra were taken on an XL-200 (Varian) spectrometer with TMS as the internal standard. Melting points were determined on a Boetius type hot plate. Experimental values for elemental analyses correspond to theor. values.

Methyl Ester of N-(β-methoxycarbonylpropionyl)cysteine (II). To a suspension of 1.71 g (0.01 mole) of Ic in 15 ml of $CHCl_3$ at 20-25°C we sequentially add 1.01 g (0.01 mole) of

$Et_3N$, 1.32 g (0.01 mole) of the monomethyl ester of succinic acid [13], and a solution of 2.06 g (0.01 mole) of dicyclohexylcarbodiimide in 10 ml of $CHCl_3$. The mixture is stirred at the same temp. for 9 h and the precipitate is separated by filtration and washed with 20 ml of $CHCl_3$. The filtrate is extracted with water (4 × 50 ml), the chloroform layer is dried and evaporated, and the residue is ground with petroleum ether, yielding 1.73 g (69%) of compound II, mp 154-155°C (MeOH), $M^{+\cdot}$ 249, $C_9H_{15}NO_5S$. NMR spectrum ($CDCl_3$), δ, ppm: 2.62 multiplet (m) (4H, $CH_2CH_2$), 3.20 doublet (d) (2H, $CH_2CH$, $^3J_{CH_2CH}$ = 5.3 Hz), 3.70 singlet (s) (3H, $COOCH_3$), 3.78 s (3H, $COOCH_3$), 4.87 quartet (q) (1H, CH), 6.74 d (1H, NH, $^3J_{NH,CH}$ = 7.6 Hz).

Hydrochloride of 2-Phenyl-4-carboxy-5,5-dimethylthiazolidine (IVg). To a solution of 0.745 g (5 mmoles) of D-penicillamine in 10 ml water at 0°C we did dropwise 1.59 g (0.015 mole) of benzaldehyde. The mixture is stirred for 3 h at 25°C and the precipitate is separated by filtration, washed with abs. ethanol, and dried, yielding 1 g (85%) of IVg, mp 155-157°C, $M^+$ 237 (mp in the literature is 151.5-152°C [14]).

To 1.5 g of the base in 10 ml of methanol is added 10 ml of a methanol solution of HCl, followed by 10 ml of abs. ether, and the precipitate is filtered off, giving 1.2 g (69%) of the hydrochloride of IVg, mp 160-161°C (ethanol) (literature mp for the racemate is 172-173°C [14]). $C_{12}H_{16}ClNO_2S$.

Hydrochloride of 3-Piperidinoacetyl-4-methoxycarbonylthiazolidine (VIa). To 1.12 g (5 mmoles) of 3-chloracetyl-4-methoxycarbonylthiazolidine (VIIb) dissolved in 10 ml of hot isopropanol we add 0.85 g (0.01 mole) of piperidine dropwise and let the mixture remain at 25°C for 24 h. The precipitate is filtered off, the filtrate evaporated, and then 30 ml of abs. ether is added and the resulting precipitate is filtered off. A methanol solution of HCl is added to the filtrate until the pH reaches 2.0 and the precipitate is filtered off. After drying in a desiccator, 1.03 g (67%) of compound VIa is obtained, mp 195-196°C (i-PrOH), $M^{+\cdot}$ 272. $C_{12}H_{21}ClN_2O_3S$.

Hydrochloride of 3-(N-Methylpiperazino)acetyl-4-methoxycarbonylthiazolidine (VIb). To 1.12 g (5 mmoles) of VIIb dissolved in 10 ml of hot isopropanol we add 1 g (0.01 mole) of N-methylpiperazine and let the mixture stand for 2 days at 20-25°C. The solution is then concentrated by evaporation and abs. ether is added to the remainder, the ether layer is decanted, and a methanol solution of HCl is added dropwise. The precipitate is filtered off and dried in a dessicator, yielding 0.6 g (33%) of compound VIb, mp 183-186°C (MeOH), $M^+$ 287. $C_{12}H_{21}N_3O_3S \cdot 2\ HCl \cdot 0.5\ H_2O$.

3-Chloroacetyl-4-methoxycarbonylthiazolidine (VIIb). To a mixture of 7.35 g (0.05 mole) of 4-methoxycarbonylthiazolidine and 5.05 g (0.05 mole) of $Et_3N$ in 40 ml of anhydrous benzene at o°C we add 11.3 g (0.1 mole) of chloroacetyl chloride dropwise with stirring for 2 h at 0-5°C. The precipitate is filtered off and washed with anhydrous benzene, the filtrate is evaporated in vacuo, and 30 ml of abs. ether is added to the residue. The precipitate is then filtered off. We obtain 9 g (80%) of VIIv, mp 58-59°C (i-PrOH), $M^{+\cdot}$ 223. $C_7H_{10}ClNO_3S$. (Literature mp for 3-chloroacetyl-DL-4-methoxycarbonylthiazolidine is 52-55°C [24]).

Hydrochloride of 3-Morpholinoacetyl-4-methoxycarbonylthiazolidine (VIc). To 3.36 g of VIIb dissolved in 30 ml of hot isopropanol we add 2.61 g of morpholine dropwise and the mixture is stirred for 0.5 h at 25°C. Following evaporation, 50 ml of abs. ether are added to the residue, the precipitate is filtered off, and a methanol solution of HCl is added to the filtrate. The resulting precipitate is filtered off and dried in a desiccator, yielding 3.38 g (73%) of compound VIc, mp 204-206°C (MeOH). $C_{11}H_{19}ClN_2O_4S$.

2,2-Dimethyl-3-benzoyl-4-methoxycarbonylthiazolidine (VIIc). To a mixture of 2.11 g (0.01 mole) of IVd and 2.02 g (0.02 mole) $Et_3N$ in 20 ml of abs. benzene at 25°C we add 1.4 g (0.01 mole) of benzoyl chloride dropwise and the mixture is boiled for 1.5 h, cooled, and filtered. The filtrate is evaporated, the residue is washed with petroleum ether and ground with ethyl acetate. The precipitate is then filtered off, yielding 0.89 g (32%) of VIIc, mp 101-102°C (heptane) (literature mp for 2,2-dimethyl-3-benzoyl-4-methoxycarbonylthiazolidine is 105-106.5°C [17]). $C_{14}H_{17}NO_3S$.

TABLE 2. Effect of Cysteine and Thiazolidine Derivatives on Pain Sensitivity Threshold in Mice Using Various Types of Pain Stimulation (internal dose equal to 10% of $LD_{50}$)

| Compound | Increase in latent period of pain response (in % to initial level) | | % Suppression of "spasm" caused by 10% $CH_3COOH$ | $LD_{50}$, mg/kg, internal |
|---|---|---|---|---|
| | Hot plate | Tail flick | | |
| Ic | +15 | 0 | −21 | 1000 |
| III | 0 | 0 | 0 | 500 |
| II | +10 | +12 | −17 | 1000 |
| IVa | +34* | +48* | −31* | 300 |
| IVb | 0 | 0 | 0 | 300 |
| VIIa | 0 | −15 | +13 | 1000 |
| VIII | +23* | +10 | −58* | 1000 |
| VIIb | 0 | 0 | 0 | 750 |
| VIa | +25* | 0 | −20 | 1000 |
| VIb | +10 | 0 | −48* | 1000 |
| VIc | 0 | 0 | 0 | 1000 |
| IVc | 0 | 0 | −14 | 1000 |
| IVd | −25* | −50* | +26* | 500 |
| IVd 100 mg/kg | +16 | +21 | −25* | |
| IVd 200 mg/kg | +65* | +40 | −47* | |
| IVd 200 mg/kg + + naloxone** | 0 | 0 | 0 | |
| Va | 0 | 0 | 0 | 1000 |
| VIIc | +36* | +41* | −27* | 1000 |
| IVd | −12 | 0 | 0 | 1000 |
| IVf | −17 | −15 | +21 | 1000 |
| IVf 200 mg/kg | +21 | +20 | −20 | |
| IVf 300 mg/kg | +39* | +31* | −38* | |
| IVf 300 mg/kg + naloxone** | 0 | 0 | 0 | |
| Vb | 0 | 0 | 0 | 500 |
| IVg | 0 | 0 | 0 | 1000 |
| Captopril, 25 mg/kg (sc) | +40* | +25* | −28* | 2500 |

*Difference from control significant at $P < 0.05$.
**Naloxone dose is 2.5 mg/kg, given subcutaneously (sc).

## EXPERIMENTAL (BIOLOGICAL)

Derivatives of cysteine (Ic-III) and thiazolidine (IV-VIII)* were examined for their antihypertensive activity, effect on ACE in vitro, ability to inhibit the development of pressor response of arterial pressure (AP) to administration of angiotensin I (A-I), and ability to amplify and prolong the depressor effect of bradykinin (BK) [11] as well as for their analgesic activity [12, 16, 18]. Acute toxicity of these compounds when administered internally was also determined [23].

The results were subjected to statistical treatment by determining mean values and SD; the Student's t-criterion was used to compare mean values.

The effects of compounds Ic-VIII compared to cysteine (Ia) and captopril on AP in rats with different hypertension models, on the pressor effect of A-I, on the depressor effect of BK, and on ACE activity are presented in Table 1.

As Table 1 shows, compounds Ic, IVd, and IVf exerted an antihypertensive effect, causing a significant decrease in AP compared to control. In addition, these three compounds inhibited the pressor response to A-I by 16, 35, and 30%, respectively, and amplified and prolonged the depressor action of BK by 40, 90, and 100%, respectively. Compounds Ic, IVd, and IVf also inhibited ACE to a degree comparable with cysteine but less than the inhibition shown by captopril.

*Compounds Ic, III, IVb-d, f, g, and VIa-c are studied as their hydrochloride salts.

It should be noted that the antihypertensive effect of the compounds was brief: AP returned to the initial value 1-2 h after administration of the compound (the antihypertensive action of captopril at the dosage used lasted 4-5 h).

Along with compounds having BK-positive properties, BK-negative compounds were observed, i.e., compounds that diminish the effect of BK. Compounds VIII and VIIc decreased the depressor response to BK to 40%, and compounds IVa and VIb decreased it to 80 and 70%, respectively, of the initial level. The remaining compounds had little activity with respect to BK effect.

Table 2 presents data regarding the acute toxicity when given internally and the effect of compounds I-VIII on pain reactions in mice.

Table 2 shows that the majority of compounds examined have low toxicity (according to the classification in [7]) and a number of them have elements of analgesic activity (compounds II, IVa, VIII, VIb, and VIIc). It should be noted that BK-negative compounds (IVa, VIII, VIb, and VIIc) showed an analgesic effect, especially that expressed in the model of acetic acid "spasms." Compounds IVd and IVf, which inhibit ACE and have BK-positive properties at doses equal to 10% of the $LD_{50}$, amplify the nociceptive reaction. However, at increased doses these compounds show analgesic properties that are blocked by prior administration of the opiate antagonist naloxone, which indicates the possible involvement of endogenous opioid peptides in the realization of the analgesic effect of the compounds.

Structure-activity analysis in this chemical series showed several interesting features: the presence of a hydrazide moiety and a thiazolidine ring (compounds III, II, and IVa) causes the appearance of BK-negative properties and a loss of antihypertensive activity. Analogous changes in pharmacological properties were also observed when various substituents were introduced at position 3 of the thiazolidine ring (compounds VIb and VIIc). The introduction of a substituent in position 2 of the thiazolidine ring results in antihypertensive activity in compounds IVd and IVf, which is associated to a certain extent with ACE inhibition .

Thus, among thiazolidine derivatives compounds were observed which are inhibitors of angiotensin-I-converting enzyme, have antihypertensive properties, and show BK-positive activity. Compounds which have BK-positive properties can evoke an amplification of nociceptive reactions as well as an anlgesic effect, depending on the dose. Analgesia appears at compound doses that are 2-3-fold higher than those necessary for an antihypertensive effect. The elimination of analgesia by prior administration of naloxone suggests the possible participation of endogenous opioid peptides (under conditions of inhibition of their inactivation) in the realization of the analgesic effect of these compounds.

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# SYNTHESIS AND ANTIVIRAL ACTIVITY OF 7-OXO- AND 7-HYDROXY-4,5,6,7-TETRAHYDROBENZO[b]THIOPHENE DERIVATIVES

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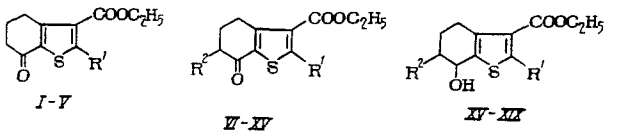
Continuing our research [1, 2] in series of benzo[b]thiophene derivatives in order to search for substances that have biological activity we have synthesized 6-substituted 7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophenes. Compounds that have antiviral activity have been previously detected among carbinols of the thiophene series [4]. The introduction of a phenylthiomethyl group into the 2 position of the indole molecule also leads to the development of antiviral activity [3]. In this connection we obtained 4,5,6,7-tetrahydrobenzo[b]thiophene derivatives that contain a phenylthio group and a hydroxy group.

In the bromination of I-IV we isolated the corresponding 6-bromo-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophenes VI-IX, the structures of which were confirmed by means of the PMR spectra. In the case of bromo derivative VI the protons of two methylene groups in the 4 and 5 positions are manifested by a multiplet at 2.48-3.16 ppm, and the signal of the proton in the 6 position shows up in the form of a triplet at 4.6 ppm.



I-V V-XV XV-XIX

$R^1$=NHAc (I, VI, X, XI, XII, XIII, XIV, XVI, XIX), NHCOEt (II, VII), $NHCOCH_2Cl$ (III, VIII), NHCOPh (IV, XI, XV, XVII), H (V, XVIII); $R^2$= N-piperidyl·HCl (XII), SCN (XIII), N-morpholyl·HCl (XI), SPh (XIV, XV, XIX), H (XVI, XVII, XVIII), Br (VI, VII, VIII, IX), I (X).

The synthesis of 2-acetamido-6-iodo derivative X was accomplished by iodinating of I with iodine chloride.

Compounds VI and IX, which contain a bromine atom in the 6 position, readily undergo nucleophilic substitution with reagents such as secondary amines, potassium thiocyanate, and thiophenol to give the corresponding 6-substituted 7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophenes XI-XV. An absorption band that is characteristic for the thiocyanato group at 2165 $cm^{-1}$ appears in the IR spectrum of derivative XIII.

7-Hydroxy derivatives XVI-XIX are formed in high yields in the reduction of 7-oxo-derivatives I, IV, V, and XIV with sodium borohydride. An absorption band of a hydroxy group at 3620 $cm^{-1}$ appears in the IR spectra of XVI-XIX recorded from solutions in $CCl_4$.

The PMR spectrum of XIX confirms the proposed structure. Signals of substituents in the 2 and 3 positions are present in the spectrum: a $COCH_3$ singlet at δ 2.24 ppm, a triplet and

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