Communications to the Editor

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New Sulfhydryl Compounds with Potent Antihypertensive Activities

(4*R*)-3-(Mercaptoacyl)-4-thiazolidinecarboxylic acids (III) were synthesized and their inhibitory activities against angiotensin-converting enzyme (ACE) were examined *in vitro* and *in vivo*. (4*R*)-3-[(2*S*)-3-Mercapto-2-methylpropanoyl]-4-thiazolidinecarboxylic acid (**4a**) was the most potent orally active inhibitor of ACE among the derivatives and its activity was almost same as that of (2*S*)-1-[(2*S*)-3-mercapto-2-methylpropanoyl]proline (**8**).

Keywords——thiol; amino acid; (4*R*)-3-[(2*S*)-3-mercapto-2-methylpropanoyl]-4-thiazolidinecarboxylic acid; thiazolidinecarboxylic acid; diastereoisomer acyl amino acid; angiotensin-converting enzyme inhibitor; antihypertensive agent

We synthesized numbers of N-mercaptoacyl-(*R*)-cysteine derivatives in a series of synthetic studies on sulfhydryl compounds, and some of their pharmacological activities were determined.[1] Recently, it was suggested that (2*S*)-1-[(2*S*)-3-mercapto-2-methylpropanoyl]-proline (SQ14225), a potent inhibitor of angiotensin-converting enzyme (ACE), might be useful as a diagnostic or therapeutic agent for renal hypertension.[2] Thus a preliminary study was performed in an attempt to know the effects of the cysteine derivatives on ACE activity and it was clarified that one of the derivatives, (2*R*)-N-[(2*S*)-2-mercaptopropanoyl]cysteine (**7**), produced the inhibitory action on ACE though the activity of **7** was considerably lower than that of (2*S*)-1-[(2*S*)-3-mercapto-2-methylpropanoyl]proline (**8**). In addition, (4*R*)-4-thiazolidinecarboxylic acid (I) prepared from L-cysteine bears structural resembrance to L-proline. These findings prompted us to synthesize (4*R*)-3-(mercaptoacyl)-4-thiazolidinecarboxylic acids (III). In this communication we describe the synthesis of III and their inhibitory activities against ACE.

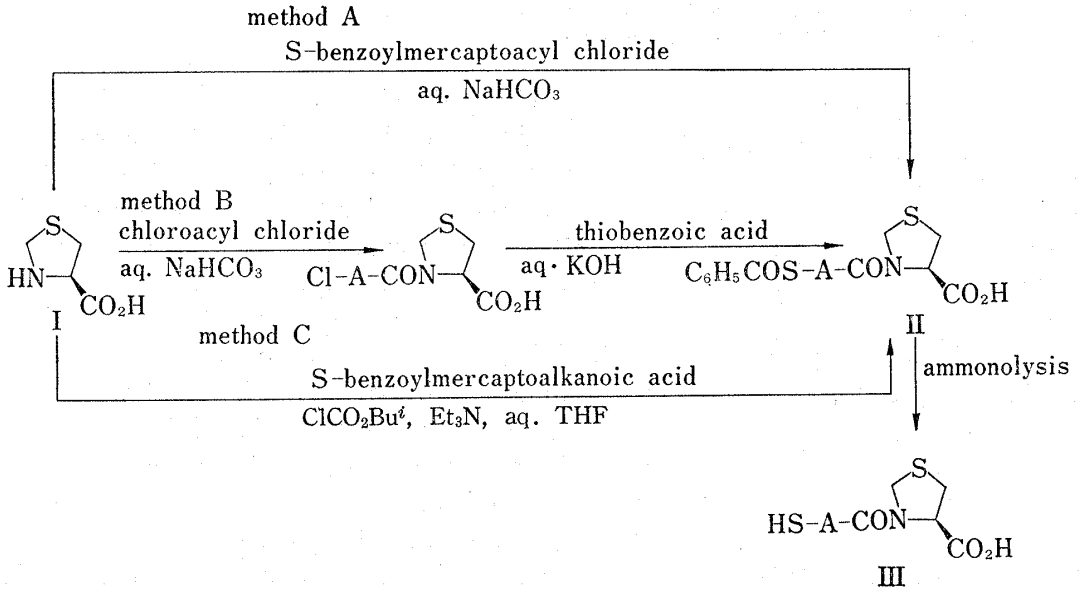
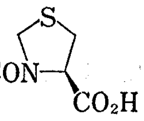


Chart 1

1) T. Fujita, M. Oya, H. Takashina, and T. Iso, Ger. Offen., 2709820 (1977).
2) M.A. Ondetti, B. Rubin, and D.W. Cushman, *Science*, **196**, 441 (1977).
3) M.A. Ondetti and D.W. Cushman, Japan. Kokai, **77** 116456 (1977).

Table I. Physical Constants and Inhibitory Activities against ACE of (4*R*)-3-(Mercaptoacyl)-4-thiazolidinecarboxylic Acids (III)

Compd.[a] HS-A-CON  A	Prepn. method of II	mp (°C)	$[\alpha]_D^{25}$ in MeOH (°, *c*)	AI[e] (IC_{50})	BK[e] (AC_{50})	ACE[e] (IC_{50})
1 $-CH_2-$	A, B	115—122	−137.9, 1	7.0	0.097	12.0
2a $-CH(CH_3)-$	A, C	122—123	−110.4, 1	0.37	0.019	0.46
2b		161—163	−166.2, 1	7.0	0.34	27.0
3 $-(CH_2)_2-$	A	112—114	−126.0, 1	2.4	0.037	10.0
4a $-CH_2CH(CH_3)-$	A, C	113—114	−175.0, 1	0.16	0.0035	0.26
4a-DCHA[b]		190—191	−116.1, 1			
4b		oil	−81.5, 1	4.8	0.035	1.3
4b-DCHA[b]		179—180	−84.5, 1			
5a $-CH(CH_3)CH_2-$	A	103—106	−116.0, 1.6	8.0	0.22	8.6
5b		oil	−90.6, 2.5	80.0	0.68	91.0
5b-DCHA[b]		192—193.5 (dec.)				
6 $-(CH_2)_3-$	A	oil	−135.2, 2.6	130.0	5.2	600.0
6-DCHA[b]		166—167.5 (dec.)				
7 (2*R*)-N-[(2*S*)-2-Mercaptopropanoyl]cysteine	A	114—115	+3.5, 2[d]	3.0	0.35	8.0
8 (2*S*)-1-[(2*S*)-3-Mercapto-2-methylpropanoyl]proline	A	88— 89[c]	−131.0[c], 2[d]	0.21	0.0036	0.081
9 Bradykinin potentiating peptide B				9.3	0.6	3.1
10 L-Cysteine				>300	1000.0	6100.0
11 Glutathione				>300	140.0	1900.0

a) **2b, 4b** and **5b** are diastereoisomers of **2a, 4a** and **5a** respectively.
b) Dicyclohexylamine.
c) Physical constants of **8** in ref. 3 are 103—105° (mp) and −131° ($[\alpha]_D$, *c*=2, EtOH).
d) In EtOH.
e) Inhibitory activities of the compounds against ACE were determined according to the procedures in ref. 2 (AI; angiotensin I, BK; bradykinin). IC_{50}; micromolar concentration of compound producing 50% inhibition of the enzyme activity or agonist effect. AC_{50}; micromolar concentration of compound producing 50% augmentation of agonist effect.

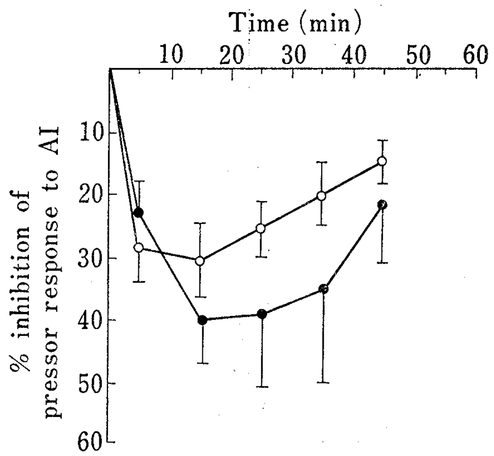


Fig. 1. Inhibitory Effects of **4a** and **8** on Pressor Response to AI of Unanesthetized Rats

AI was administered intravenously at the indicated times in a dose of 310 ng/kg. Results are the mean ±S.E. obtained from the three experiments.
—○—: 4a, 0.3 mg/kg (*p.o.*)
—●—: 8, 0.3 mg/kg (*p.o.*)

The synthesis of III was accomplished by three procedures (method A, B and C) shown in Chart 1. When (4*R*)-3-(S-benzoylmercaptoacyl)-4-thiazolidinecarboxylic acids (II) have two diastereoisomers, both isomers were separated by recrystallization or column chromatography.

Some of the physical constants and inhibitory activities of these compounds against ACE are summarized in Table I. (4*R*)-3-[(2*S*)-3-Mercapto-2-methylpropanoyl]-4-thiazolidinecarboxylic acid (**4a**) was the most potent inhibitor of ACE isolated from rabbit lung among the derivatives-synthesized in the present study. The compound also inhibited the contractile response of isolated guinea-pig ileum to angiotensin I (AI, 100 ng/ml) and augmented the response to bradykinin (BK, 5 ng/ml), while it did not produce any effect on the responses to angiotensin II (10 to 30 ng/ml) and acetylcholine (10 to 30 ng/ml).

Moreover, as shown in Fig. 1, **4a** in lower oral dose of 0.3 mg/kg inhibited significantly the pressor response to AI (310 ng/kg, *i. v.*) of unanesthetized rats. The inhibitory activities of **4a** *in vitro* and *in vivo* were almost same as those of **8**. These data suggest the usefulness of **4a** as a diagnostic or therapeutic agent for the renal hypertensive disease. In addition, structure activity relationship restricted to mercaptoacyl moiety of the thiazolidine derivatives was as follows: 3-mercapto-2-methylpropanoyl>2-mercaptopropanoyl>3-mercaptopropanoyl>3-mercaptobutanoyl>4-mercaptobutanoyl. In this respect, further evaluation is now in progress.

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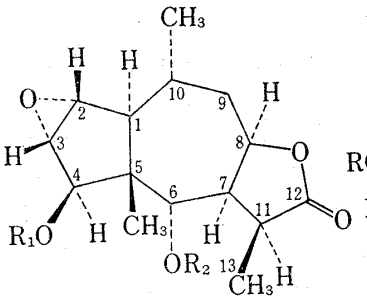
Isolation and Structure Determination of 4-*O*-Tigloyl-11,13-dihydroautumnolide, a New Sesquiterpene Lactone from North Carolina *Helenium autumnale* L.

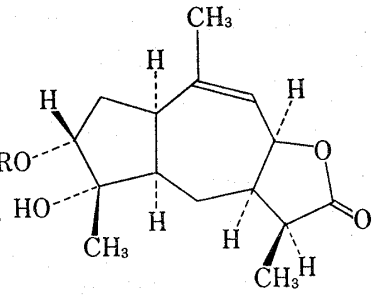
The structure and relative stereochemistry of 4-*O*-tigloyl-11,13-dihydroautumnolide (I), a new pseudoguaianolide sesquiterpene lactone from North Carolina *Helenium autumnale* L., have been determined on the basis of spectroscopic data, chemical transformation, and single-crystal X-ray analysis.

Keywords——4-*O*-tigloyl-11,13-dihydroautumnolide; sesquiterpene lactone; *Helenium autumnale* L.; X-ray analysis; structure determination

As a consequence of our continuing investigations of the terpenoid fraction of an extract from *Helenium autumnale* L. collected in North Carolina, U. S. A.,[1] we here report on the iso-



I : R_1= tiglyl, R_2=H
IV : R_1= tiglyl, R_2=$COCH_3$
V : R_1=R_2=H



II : R=H
III : R= angelyl

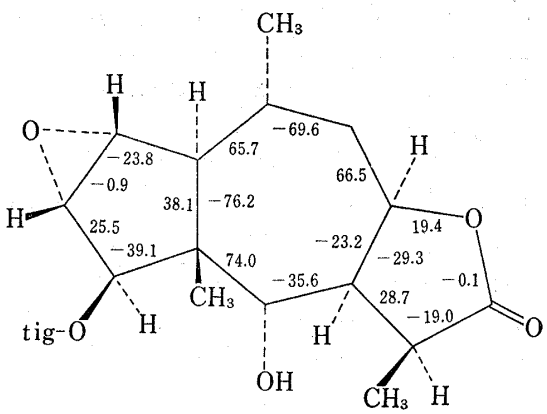


Fig. 1. Endocyclic Torsion Angles (Deg.) in (I)

1) A.T. McPhail, K.D. Onan, H. Furukawa, and K.H. Lee, *Tetrahedron Lett.*, **1975**, 1229; A.T. McPhail, P.A. Luhan, K.H. Lee, H. Furukawa, R. Meck, and C. Piantadosi, *Tetrahedron Lett.*, **1973**, 4087; H. Furukawa, K.H. Lee, T. Shingu, R. Meck, and C. Piantadosi, *J. Org. Chem.*, **38**, 1722 (1973).