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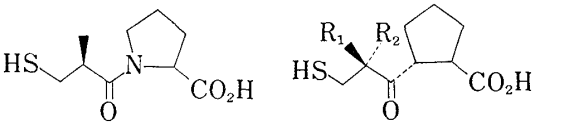
Synthesis of Carbocyclic Analogs of Captopril (SQ-14225)[1]

Carbocyclic analogs of captopril (SQ-14225, I), an angiotensin-converting enzyme (ACE) inhibitor, were synthesized starting from methyl cyclopentenoate (III) in order to examine their inhibitory activity of ACE.

Keywords——cyclopentane; angiotensin-converting enzyme; enzyme inhibitor; captopril (SQ-14225); conjugate addition

In 1977, Ondetti and his collabolators developed a new class of potent and specific inhibitors of angiotensin-converting enzyme (ACE) designing the active structures based on their hypothetical model of the active site of ACE,[2] and captopril (I, SQ-14225), the most potent substance among them, is now shown to possess clinical usefulness as an oral active antihypertensive agent.[3]



I

IIa : $R_1=CH_3$, $R_2=H$
IIb : $R_1=H$, $R_2=CH_3$

Fig. 1

Consideration of their hypothetical model has tempted us to synthesize carbocyclic analogs (II) in which the proline moiety of I is replaced by a cyclopentanecarboxilic acid moiety, since the nitrogen part of I was postulated not to participate in binding of ACE. Here we wish to report a fairly short-step synthesis of the title compounds.[4]

The Michael reaction of lithio derivative of methyl 1-(methylthio)-propyl sulfoxide[5] (IV) to methyl cyclopentane carboxylate (III) was smoothly carried out at −78° to yield the conjugate addition product (V), which was then hydrolyzed by treating with a small amount of 9 N sulfuric acid in aqueous acetone, followed by the fractional distillation to give the ketone (VI) in 46% yield from III. [bp 127—130° (18 mmHg), IR ν_{max}^{film} cm^{-1}; 1730, 1710, PMR δ (CCl_4); 3.60 (3H, s), 2.50 (2H, q) 1.00 (3H, t)].

A mixture of 30% aqueous formaldehyde, dimethyl amine hydrochloride and the ketone (VI), was heated at reflux to give the dimethyl aminomethylketone (VII) [IR ν_{max}^{film} cm^{-1}; 2860, 2810, 2760, 1730, 1710, PMR δ (CCl_4); 3.63 (3H, s), 2.13 (6H, s), 1.00 (3H, J=6 Hz)], which underwent decomposition by further heating to yield methyl methacryloyl cyclopentane carboxylate (VIII) [IR ν_{max}^{film} cm^{-1}; 1735, 1675, 1630, PMR δ (CCl_4); 5.92 (1H, m), 5.75 (1H, m) 3.63 (3H, s), 1.83 (3H, s)].

Introduction of mercapto group to VIII was achieved by conjugate addition with thiol acetic acid to give a mixture of an almost equal amount of the diastereoisomers (IX) [IR ν_{max}^{film} cm^{-1}; 1735, 1710, 1690, PMR δ (CCl_4); 3.65, 3.63 (two singlets), 1.15, 1.13 (two doublets), MS m/e: 273 (M^++1), 197 (M^+–$SCOCH_3$)].

1) Synthetic Studies on Cyclopentane Derivatives. Part XI. Preceding paper in series: *Tetrahedron Lett.*, accepted.
2) D.W. Cushman, H.S. Cheung, E.F. Sabo, and M.A. Ondetti, *Biochemistry*, **16**, 5484 (1977).
3) H. Gavras, I. Gavras, S. Textor, L. Volicer, H.R. Brunner, and E.J. Rucinska, *New Engl. J. Med.*, **298**, 991 (1978).
4) Studies along the same line were also reported quite recently by Ondetti *et al.*, Abstracts of Papers, ACS/CSJ Chemical Congress, Honolulu, Hawaii, April 5, 1979, MEDI 64.
5) Prepared from lithio derivative of methylthiomethyl methylsulfoxide and ethylbromide (*cf.*, K. Ogura and G. Tsuchihashi, *Tetrahedron Lett.*, **1971**, 3151).

When thiolbenzoic acid was employed as a thiolating agent, the desired thiolbenzoate (Xa)[6] was obtained as a major component along with the isomeric minor one (Xb) (the ratio; *ca.*, 2: 1) [IR ν_{max}^{film} cm^{-1}; 1730, 1710, 1660 for both Xa and Xb, PMR δ (CCl_4); 3.62 (3H, s) 1.22 (3H, d, J=6 Hz) for Xa and 3.55 (3H, s), 1.20 (3H, d, J=6 Hz) for Xb].

Hydrolysis of IX with 1 N-sodium hydroxide yielded a mixture of the mercapto acid (IIa) and (IIb), which could be separated by column chromatography on silica gel [IR ν_{max}^{film} cm^{-1}; 2700—2500, 1710—1700, PMR δ ($CDCl_3$); 9.8 (1H), 1.15 (3H, d, J=6 Hz) for both IIa and IIb, TLC *Rf*: 0.41 for IIa, 0.50 for IIb (silica gel, AcOEt)].

The carbocyclic analog (IIa) obtained here was shown to possess some significant ACE inhibitory activity,[7] and the present result might give some support to the hypothesis proposed by Ondetti *et al.*

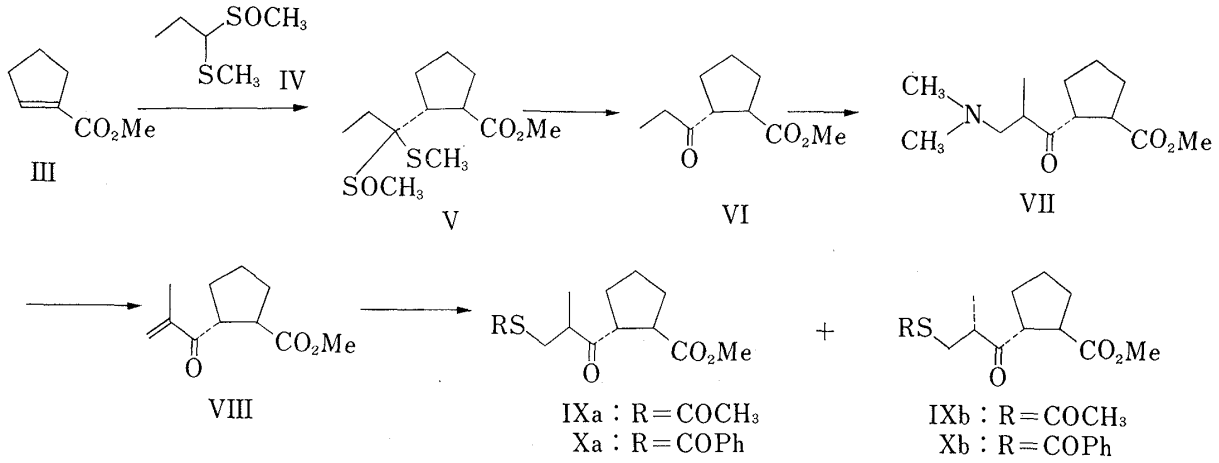


Fig. 2

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6) Configurational assignment of II was based on biological activities.
7) Inhibitory activities (IC_{50}) were measured by the method of the contractile response of guinea pig ileum to angiotensin I (B. Rubin, R.J. Laffan, D.G. Kotler, E.H. O'Keefe, D.A. Demaio, and M.E. Goldberg, *J. Pharmacol. Exp. Ther.*, **204**, 271 (1978): 23 μM for IIa [tromethamine salt, $(HOCH_2)_3CNH_2$; water soluble salt form] and 0.14 μM for captopril (free acid from) and 0.39 μM for captopril (tromethamine salt form). On the other hand, the configurational isomer (IIb) has much less activity than IIa in the same measurement (IC_{20}=46 μM, tromethamine salt form).
8) The author to whom correspondence should be addressed.