# Bicyclic Lactam Inhibitors of Angiotensin Converting Enzyme

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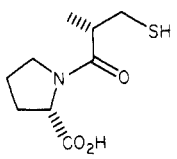
Syntheses of the potent angiotensin converting enzyme inhibitor 1-(carboxymethyl)-3-(mercaptomethyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (**4a**) and the corresponding eight-membered ring analogue (**4b**) are described. The influence of ring size on the inhibitory potencies of these substances is discussed.

Captopril (1) is a potent, orally effective inhibitor of



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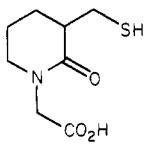

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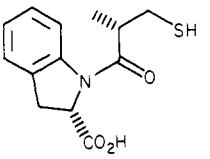

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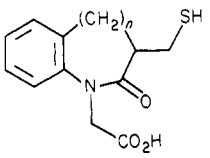


**4a**, $n = 2$
**b**, $n = 3$

angiotensin converting enzyme (dipeptidyl carboxypeptidase, E.C. 3.4.15.1) that has become established as an agent useful for the treatment of hypertension and congestive heart failure.[2] A significant incidence of side effects is associated with captopril therapy,[2] and, consequently, it seemed desirable to prepare more potent inhibitors that might offer a greater therapeutic ratio. The approach we elected to follow involved the synthesis of conformationally restricted analogues, as hopefully this would also provide new information about the mode of binding of inhibitors and substrates to the enzyme.

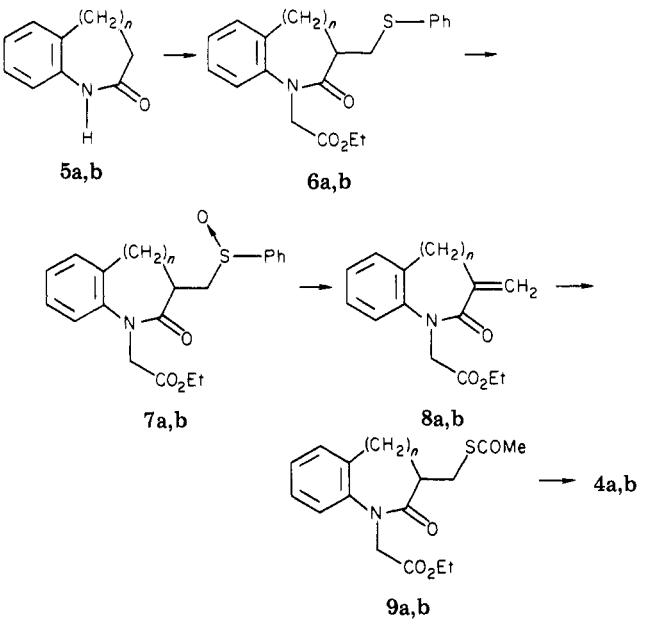
We first prepared compound **2**, the synthesis of which has now been described by two groups.[3] This substance is a relatively weak angiotensin converting enzyme inhibitor (see Table I). We realized that **2** corresponds to a conformation of captopril in which severe nonbonded interactions would occur because of the close proximity of the methyl group and C-5 of the pyrrolidine ring. Analogues with a seven- or eight-membered ring would clearly correspond to more reasonable conformations of captopril, and, indeed, a recent communication[4] suggests this to be the case (see Table I). In addition, we were aware that the indoline analogue **3**[5] was more potent than **1** (see Table I). We therefore decided to prepare the bicyclic lactams **4a,b**.

Table I. Inhibitors of Angiotensin Converting Enzyme

| no. | $IC_{50}$, nm |
|---|---|
| 1 | 15,[a] 23[c] |
| 2[b] | 1500, 3400[c] |
| 3 | 2.6[d] |
| 4a[b] | 9 |
| 4b[b] | 4 |
| 10a[b] | 170[c] |
| 10b[b] | 53[c] |

[a] This corresponds to the value reported in reference 5b. [b] Racemate. [c] Data from ref 4. [d] Data from ref 5.

Scheme I[a]



[a] a, $n = 2$; b, $n = 3$.

**Chemistry.** The syntheses of **4a,b** are summarized in Scheme I. The key reaction in the sequence is the regioselective dialkylation of the N,$\alpha$-dianion of **5a,b**[6,7] with iodomethyl phenyl sulfide,[8] followed by ethyl chloroacetate. Numerous examples of amide dianion alkylation reactions have been reported,[9] but these appear to be the first examples in which the dianion has been dialkylated regioselectively by sequential addition of two electrophiles. The thioethers **6** were oxidized to sulfoxides **7**, which on thermolysis gave the $\alpha,\beta$-unsaturated lactams **8**. Addition of thiolacetic acid and removal of the protecting groups completed the syntheses.

(1) Present address: Department of Chemistry, Iona College, New Rochelle, NY 10801.
(2) Heel, R. C.; Brogden, R. N.; Speight, T. M.; Avery, G. S. *Drugs* **1980**, *20*, 409. Romankiewicz, J. A.; Brogden, R. N.; Heel, R. C.; Speight, T. M.; Avery, G. S. *Ibid.* **1983**, *25*, 6.
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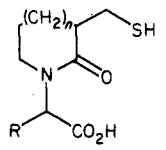
(5) (a) Kim, D. H.; Guinosso, C. J.; Buzby, G. C.; Herbst, D. R.; McCaully, R. J.; Wicks, T. C.; Wendt, R. L. *J. Med. Chem.* **1983**, *26*, 394. (b) Stanton, J. L.; Gruenfeld, N. G.; Babiarz, J. E.; Ackerman, M. H.; Friedmann, R. C.; Yuan, A. M.; Macchia, W. *Ibid.* **1983**, *26*, 1267.
(6) Briggs, L. H.; de Ath, G. *J. Chem. Soc.* **1937**, 456.
(7) Jones, D. H.; Stephenson, G. F.; Spray, G. W.; Wragg, W. R. *J. Chem. Soc. C* **1969**, 2176.
(8) Trost, B. M.; Kunz, R. A. *J. Org. Chem.* **1974**, *39*, 2648.
(9) For an example of $\alpha$-alkylation of an amide dianion, see: Gay, R. L.; Hauser, C. R. *J. Am. Chem. Soc.* **1967**, *89*, 1647.

0022-2623/84/1827-0816$01.50/0 

## Biological Results

The in vitro inhibitory activities of **4a,b** were determined, and comparative data on **1–3** were also obtained. Data for the monocyclic lactams **10a,b** are from ref 3. The results are given in Table I.



**10a**, $n = 2$; R = H
**b**, $n = 3$; R = $CH_3$

## Discussion

As indicated in Table I, the bicyclic lactams **4a,b** are potent inhibitors of angiotensin converting enzyme, and the compounds are clearly significantly more potent than the monocyclic lactams **10a,b**. It is satisfying that **4a,b** have structures that correspond to accessible conformations of captopril (**1**). However, the seven-membered compound **4a** corresponds to a conformation of indoline **3** in which the hydrogen atom on C-7 is very close to hydrogen atoms on the methyl group. The data in Table I suggest that the eight-membered lactam **4b** may be more potent than **4a** and this would imply that captopril (**1**) and the indoline (**3**) may bind to the enzyme in a conformation more compatible with the eight-membered ring structure of **4b**. This work provides confirmation of the existence of a cavity at the active site[5] that can accommodate the benzene ring portion of the inhibitors.

## Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. NMR spectra were obtained in $CDCl_3$ solution on a Varian EM-390 instrument, and mass spectra were obtained on a Hewlett-Packard HP 5985 spectrometer.

**Ethyl 3-[(Phenylthio)methyl]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepine-1-acetate (6a).** To a solution of **5a**[6] (9.0 g, 0.056 mol) in dry THF (360 mL) stirred under a dry $N_2$ atmosphere at 0 °C was added *n*-BuLi (55 mL of a 2.28 M solution in hexanes; 2.25 equiv). The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 20 min. A solution of freshly prepared iodomethyl phenyl sulfide[8] (20.9 g, 1.5 equiv) in dry THF (150 mL) was added, and stirring was maintained for an additional 1.5 h. Ethyl chloroacetate (10.3 g, 1.5 equiv) was added, and the reaction mixture was stirred for an additional 2 h. Water (50 mL) was added, and the aqueous phase was washed with $CH_2Cl_2$ (100 mL). The combined organic solutions were dried over $MgSO_4$, and the solvents were removed under reduced pressure. The residue was chromatographed on silica gel (250 mL). Elution with toluene/EtOAc (1:1) gave **6a** (12.5 g, 61%) as an oil, which crystallized on standing: mp 81–82 °C; TLC (silica gel; 5% EtOAc/toluene) $R_f$ 0.5; NMR $\delta$ 1.23 (t, 3 H, $J$ = 7.5 Hz), 2.7–3.5 (m, 7 H), 4.18 (q, 2 H, $J$ = 7.5 Hz), 4.53 (q, 2 H, $J$ = 15 Hz), 7.23 (s, 9 H); MS, $m/e$ (relative intensity) 369 ($M^+$, 20), 296 (3), 260 (20), 91 (100). Anal. ($C_{21}H_{23}NO_3S$) C, H, N.

**Ethyl 3-[(Phenylsulfinyl)methyl]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepine-1-acetate (7a).** A solution of sodium periodate (7.2 g, 0.03 mol) in water (45 mL) was added to a solution of **6a** (5.0 g, 0.014 mol) in methanol (50 mL) and THF (100 mL) at 0 °C under a $N_2$ atmosphere. After 15 min at 0 °C, the reaction mixture was stirred at room temperature for 48 h. The organic solvents were removed under reduced pressure, and water (75 mL) was added. The mixture was extracted with $CH_2Cl_2$ (2 × 150 mL), and the combined $CH_2Cl_2$ solutions were washed with water (50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give **7a** (5.2 g, 100%) as a mixture of diastereomers, which was not further purified: NMR $\delta$ 1.2 (2 t, 3 H), 2.0–3.4 (m, 7 H), 4.0–4.5 (m, 4 H), 7.0–7.7 (m, 9 H).

**Ethyl 3-Methylene-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepine-1-acetate (8a).** A solution of **7a** (4.60 g, 0.012 mol) in toluene (120 mL) was refluxed for 72 h. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (100 g). Elution with toluene/EtOAc (5:1) gave **8a** (1.83 g, 59%) as an oil: TLC (silica gel; 5% EtOAc/toluene) $R_f$ 0.65; NMR $\delta$ 1.20 (t, 3 H), 3.90 (m, 4 H), 4.17 (q, 2 H), 4.60 (s, 2 H), 4.90 (s, 1 H), 5.23 (s, 1 H), 7.27 (s, 4 H).

**3-(Mercaptomethyl)-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepine-1-acetic Acid (4a).** A solution of **8a** (1.50 g, 0.0058 mol) and thiolacetic acid (3 mL) in dichloromethane (20 mL) was maintained at room temperature for 18 h. The reaction mixture was poured into ice-cold 5% aqueous $NaHCO_3$ (50 mL) and stirred for 10 min at 0 °C. $CH_2Cl_2$ (30 mL) was added, and the organic layer was washed with 5% aqueous $NaHCO_3$ (25 mL) and water (5 × 25 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave **9a** as an oil, which was directly converted to **4a**. A solution of sodium hydroxide (1.0 g, 0.025 mol) in deoxygenated water (6 mL) was added to a solution of **9a** (1.7 g, 0.005 mol) in deoxygenated methanol (10 mL). The reaction mixture was stirred at room temperature for 4 h under a $N_2$ atmosphere. The workup was also carried out under a $N_2$ atmosphere. The reaction mixture was poured into 1 N HCl (200 mL), and the solution was extracted with $CH_2Cl_2$ (5 × 100 mL). The combined organic solutions were dried over $MgSO_4$ to give **4a** (1.03 g, 67% from **8a**): NMR $\delta$ 1.8–3.3 (m, 8 H), 4.55 (q, 2 H), 7.25 (s, 4 H), 10.93 (s, 1 H); MS, $m/e$ (relative intensity) 265 ($M^+$, 15), 232 (30), 91 (60). The substance was converted to the dicyclohexylamine salt, mp 189–191 °C dec. Anal. ($C_{13}H_{15}NO_3S \cdot C_{12}H_{23}N$) C, H, N.

**3-(Mercaptomethyl)-3,4,5,6-tetrahydro-2-oxo-1*H*-1-benzazocine-1-acetic Acid (4b).** This substance was obtained by a sequence of reactions analogous to that used for the preparation of **4a** but starting with 3,4,5,6-tetrahydro-1*H*-1-benzazocin-2-one (**5b**).[7] Ethyl 3-[(phenylthio)methyl]-3,4,5,6-tetrahydro-2-oxo-1*H*-1-benzazocine-1-acetate (**6b**) was obtained as an oil: NMR $\delta$ 1.26 (t, 3 H, $J$ = 7.5 Hz), 1.8–2.35 (m, 7 H), 2.8 (m, 2 H), 4.20 (q, 2 H, $J$ = 7.5 Hz), 4.45 (q, 2 H, $J$ = 4.0 Hz), 7.33 (m, 9 H). Anal. ($C_{22}H_{25}NO_3S$) C, H, N. Ethyl 3-[(phenylsulfinyl)methyl]-3,4,5,6-tetrahydro-2-oxo-1*H*-1-benzazocine-1-acetate (**7b**) was obtained as a mixture of diastereomers as an oil: NMR $\delta$ 1.3 (2 t, 3 H), 1.5–2.8 (m, 9 H), 4.0–4.5 (m, 4 H), 7.0–7.7 (m, 9 H). Ethyl 3-methylene-3,4,5,6-tetrahydro-2-oxo-1*H*-1-benzazocine-1-acetate (**8b**) was obtained as an oil: NMR $\delta$ 1.25 (t, 3 H, $J$ = 6.9 Hz), 1.85–2.5 (m, 4 H), 2.85 (m, 2 H), 4.21 (d, 2 H, $J$ = 6.9 Hz), 4.52 (d, 2 H, $J$ = 3 Hz), 4.76 (d, 2 H, $J$ = 7.5 Hz), 7.27 (s, 4 H). The mercaptomethyl acid (**4b**) was characterized as the dicyclohexylamine salt: mp 160–163 °C; NMR $\delta$ 1.3–3.1 (m, 10 H), 4.48 (q, 2 H), 7.33 (s, 4 H), 10.67 (s, 1 H); MS, $m/e$ (relative intensity) 279 ($M^+$, 3), 246 (10), 232 (10), 91 (50). Anal. ($C_{14}H_{17}NO_3S \cdot C_{12}H_{23}N$) C, H, N.

**Biological Studies.** Angiotensin converting enzyme was prepared in crude solubilized form from lungs of male rabbits. Fresh lungs were freed of connective tissue and processed by the method of Das and Soffer[10] to the stage of the Nonidet-P40 extract. The extract was frozen and stored at −70 °C until used in enzyme assays.

The conditions for assay of the enzyme were adapted from a procedure described by Cheung and Cushman[11] in which histidylleucine liberated from the synthetic substrate, hippurylhistidylleucine, is quantitated. The enzyme extract was diluted to the appropriate activity with 100 mM potassium phosphate buffer (pH 8.3) containing 300 mM NaCl. Various concentrations of the test drugs, as well as 5 mM hippurylhistidylleucine, were prepared in the same buffer. The reaction medium consisted of 100 μL of test drug solution (or buffer for the control), 100 μL of 5 mM hippurylhistidylleucine (or buffer for the blank), and 50 μL of enzyme solution. The reaction was started by the addition of enzyme, continued for 30 min at 37 °C, and then terminated by the addition of 0.75 mL of 0.6 N NaOH. The samples were treated at room temperature with 100 μL of a methanolic solution of *o*-phthaldialdehyde (2 mg/mL), followed after 10 min with 100 μL of 6 N HCl. They were then read against water in

(10) Das, M.; Soffer, R. L. *J. Biol. Chem.* **1975**, *250*, 6762.
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a spectrophotometer set at 360 nm, and all readings were corrected for the blank. With the aid of a standard curve (obtained by running known amounts of histidylleucine through the assay procedure), the corrected optical densities were converted to nanomoles of histidylleucine formed during the 30-min incubation. $IC_{50}$ values were determined graphically as the concentration of test drug at which the amount of histidylleucine formed was reduced to 50% of the value found in the absence of test drug. The tabulated $IC_{50}$ values represent the average of two runs.

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**Registry No.** **4a**, 89177-61-7; **4a** (dicyclohexylamine salt), 89177-62-8; **4b**, 89177-63-9; **4b** (dicyclohexylamine salt), 89177-64-0; **5a**, 4424-80-0; **5b**, 22246-75-9; **6a**, 89177-65-1; **6b**, 89177-66-2; (*R**,*R**)-**7a**, 89177-67-3; (*R**,*S**)-**7a**, 89177-68-4; (*R**,*R**)-**7b**, 89177-69-5; (*R**,*S**)-**7b**, 89177-70-8; **8a**, 89177-71-9; **8b**, 89177-72-0; thioacetic acid, 507-09-5; ethyl chloroacetate, 105-39-5; angiotensin converting enzyme, 9015-82-1; iodomethyl phenyl sulfide, 51849-22-0.

# *Book Reviews*

**Organic Chemistry Series. Volume 3. Total Synthesis of Natural Products: The 'Chiron' Approach.** By Stephen Hanessian. J. E. Baldwin, Series Editor. Pergamon Press, United Kingdom. 1983. Flexicover: XVII + 291 pp. 15 × 23 cm. ISBN 0-08-030715-9. $20.00. Hardcover: ISBN 0-08-029247-X. $40.00.

An appropriate alternative title to this delightful, informative, and important book could easily be "Total Synthesis of Natural Products: The 'Hanessian' Approach". An early footnote describes that "According to Greek mythology, Chiron was a wise and learned centaur who tutored Achilles, Jason, Hercules and Asclepius in music, morals and medicine". Professor Hanessian provides a similar service to the readers of this book.

The author describes the utility of suitable chiral precursors, in particular carbohydrates, which are modified into 'chirons' for transformation to the chiral target molecule. 'Chirons' are generated by the retrosynthetic approach, bearing in mind a readily available chiral starting material. The success of the retrosynthetic approach is presented schematically via intermediates and reagents for over 100 natural products. The text provides a clearly written analysis of each synthesis.

The heart of the book is divided into parts/chapters based on target molecules containing: apparent carbohydrate-type symmetry/acyclics, tetrahydrofurans, tetrahydropyrans, butyrolactones and valerolactones; partially hidden carbohydrate-type symmetry/acyclics and cyclics; and hidden carbohydrate-type symmetry/carbocyclics, heterocyclics, macrolides and ansa compounds.

The table of contents and index list the natural products discussed in the text, and references are included through the first-half of 1983. The subject matter and low flexicover price make this book a necessity for graduate courses on advanced organic synthesis and for all practicing organic chemists.

*Arthur D. Little, Inc.* **Alan R. Branfman**
*Cambridge, Massachusetts 02140*

**Plants Used Against Cancer.** Edited by Jonathan L. Hartwell. Quaterman Publications, Inc., Lawrence, MA. 1982. vi + 710 pp. 16 × 24 cm. ISBN 0-88000-130-5. $75.00.

I offer this volume as a candidate for one of the most ambitious yet thorough literature compilations of our times. Between its two covers are the reprints of 11 papers published in *Lloydia* between the years 1967 and 1971 listing virtually all that had been known concerning Man's use of plants in the treatment of conditions that have been or could be construed as "cancerous". Literature citations, of which there are approximately 1000, cover the period from ca. 2900 B.C. to the mid 20th Century A.D. Arrangement is alphabetical by plant family, genus, and species (about 3000). Common names, plant parts used, preparations, and medicinal uses are tabulated. An index of genera concludes the work. While pagination of the original articles has been preserved, continuous pagination had been included as appropriate to a compilation of this size.

Those of use who have been associated with the NCI cancer-screening program since its inception and who mourn its recent passing, may treasure the volume as an historical document. Others will recognize in its pages many unsolved natural products problems.

*College of Pharmacy* **Robert F. Raffauf**
*Northeastern University*
*Boston, Massachusetts 02115*

**The Biochemical Basis of Neuropharmacology. 4th Edition.** Edited by Jack R. Cooper, Floyd E. Bloom, and Robert H. Roth. Oxford University Press, New York. 1982. x + 367 pp. 14 × 21 cm. ISBN 0-19-503094-X. $11.50.

The 4th edition of this useful text first published in 1970 has been updated to reflect recent findings in this rapidly evolving field. This edition contains a separate chapter on neuroactive peptides and endorphins. The book is recommended to both experts in the field and to those who wish to inform themselves on the present state of neuropharmacology.

**Staff**

## Books of Interest

**A Textbook of Pharmaceutical Analysis. Third Edition.** By Kenneth A. Connors. Wiley, New York. 1982. x + 664 pp. 16 × 23.5 cm. ISBN 0471-09034-4. $55.00.

**Kirk-Othmer Encyclopedia of Chemical Technology. Third Edition. Volume 24. Vitamins to Zone Refining.** Edited by Martin Grayson and David Eckroth. Wiley, New York. 1984. xxvi + 917 pp. 18.5 × 26 cm. ISBN 0471-02077-X. $185.00.