Zeneca's rosuvastatin (**129**), is due to be launched in 2002 and is forecast to achieve sales of US $2.8 billion by 2005 (168).

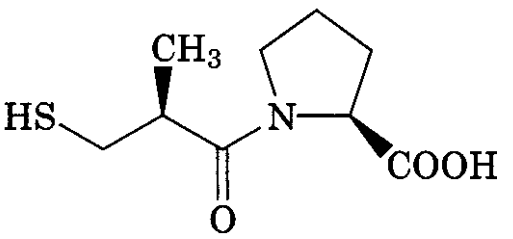
6.2 Teprotide and Captopril

While studying the physiological effects of snake poisoning, Ferreira (169) discovered that specific components in the venom of the pit viper Bothrops *jararaca* inhibited degradation of the peptide bradykinin and potentiated its hypotensive action. The "potentiating factors" proved to be a family of peptides that worked by inhibiting the dipeptidyl carboxypeptidase, angiotensin-converting enzyme (ACE) (170,171). In addition to catalyzing the degradation of bradykinin, ACE also catalyzes the conversion of human prohormone, angiotensin 1, to the potent vasoconstrictor octapeptide, angiotensin II. However, the significance of ACE in the pathogenesis of hypertension was not fully appreciated until the 1970s after Ondetti et al. (172) had first isolated and then synthesized the naturally occurring nonapeptide, teprotide (130). The compound proved to be a specific potent inhibitor of ACE and showed excellent antihypertensive properties in clinical trials, although its use was limited by the lack of oral activity.

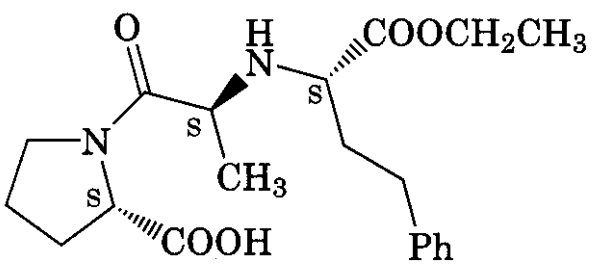
Pyr–Trp–Pro–Arg–Pro–Gln–Ile–Pro–Pro

(130)

The discovery of teprotide led to a search for new, specific, orally active ACE inhibitors. Ondetti et al. (172) proposed a hypothetical model of the active site of ACE, based on analogy with pancreatic carboxypeptidase A, and used it to predict and design compounds that would occupy the carboxy-terminal binding site of the enzyme. Carboxyalkanoyl and mercaptoalkanoyl derivatives of proline were found to act as potent, specific inhibitors of ACE and 2-D-methyl-3-mercaptopropanoyl-L-proline (**131**) (captopril) was developed and launched in 1981 as an orally active treatment for patients with severe or advanced hypertension. Captopril, modeled on the biologically active peptides found in the venom of the pit viper, made an important contribution to the understanding of hypertension and paved the way for other ACE inhibitors, such as enalapril (**132**) and lisinopril, which have had a major impact on the treatment of cardiovascular disease (173).



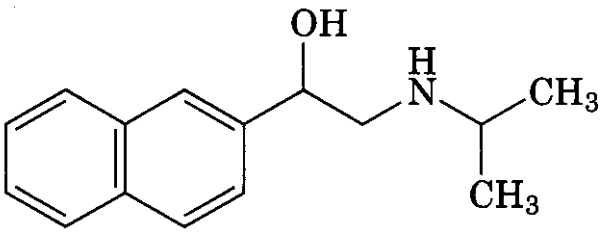
(131)



(132)

6.3 Adrenaline, Propranolol, and Atenolol

The true clinical potential of β-adrenoceptor blocking agents for treating angina, atrial fibrillation, and tachycardias was first recognized by James Black and colleagues at ICI (174). Black noted a report from Neil Moran of Emory University in 1958, showing that dichloroisoprenaline antagonized the effects of adrenaline on heart rate and muscle tension. The first effective β-adrenoceptor blocker, pronethalol (**133**), was synthesized 2 years later by the ICI group and marketed for limited use in 1963. Toxicity problems soon led pronethalol to be replaced by the 1-naphthyl analog, propranolol (**134**), which became the first β-adrenoceptor antagonist approved for general use, being more potent and yet devoid of the partial agonist or intrinsic sympathomimetic activity shown by many other analogs. Compounds with improved selectivity for the β-adrenoceptor of cardiac muscle (β-1-adreno-



(133) Pronethalol