Benazepril Synthesis (Reblogged)

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Benazepril, brand name Lotensin (Novartis), is a medication used to treat high blood pressure (hypertension), congestive heart failure, and chronic renal failure. Upon cleavage of its ester group by the liver, benazepril is converted into its active form benazeprilat, a non-sulphhydryl angiotensin-converting enzyme (ACE) inhibitor.

\[ \text{Benazepril} \]

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The reaction of 2,3,4,5-tetrahydro-1H-(1)benzazepin-2-one (I) with PCl\(_5\) in hot xylene gives 3,3-dichloro-2,3,4,5-tetrahydro-1H-(1)benzazepin-2-one (II), which is treated with sodium acetate and reduced with H\(_2\) over Pd/C in acetic acid yielding 3-chloro-2,3,4,5-tetrahydro-1H-(1)benzazepin-2-one (III). The reaction of (III) with sodium azide in DMSO affords 3-azido-2,3,4,5-tetrahydro-1H-
(1)benzazepin-2-one (IV), which is condensed with benzyl bromoacetate (V) by means of NaH in DMF giving 3-azido-1-(benzyloxy carbonyl methyl)-2,3,4,5-tetrahydro-1H-(1)benzazepin-2-one (VI). The treatment of (VI) with Raney-Ni in ethanol-water yields 3-amino-1-(benzyloxy carbonyl methyl)-2,3,4,5-tetrahydro-1H-(1)benzazepin-2-one (VII), which is debenzylated by hydrogenation with H₂ over Pd/C in ethanol affording 3-amino-1-(carboxymethyl)-2,3,4,5-tetrahydro-1H-(1)benzazepin-2-one (VIII). Finally, this compound is condensed with ethyl 3-benzylpyruvate (IX) by means of sodium cyanoborohydride in methanol acetic acid.

Scheme 1:
The reaction of 3-bromo-1-phenylpropane (I) with KCN gives 4-phenylbutyronitrile (II), which is hydrolyzed to the corresponding butyric acid (III). The cyclization of (III) with polyphosphoric acid affords 1-tetralone (IV), which is brominated to 2-bromo-1-tetralone (V) and treated with hydroxylamine to give the oxime (VI). The Beckman rearrangement of (VI) yields 3-bromo-2,3,4,5-tetrahydro-1H-(1)benzazepin-2-one (VII), which is treated with sodium azide to afford the azide derivative (VIII). The N-alkylation of (VIII) with ethyl bromoacetate (IX) by means of KOH and tetrabutylammonium bromide in THF gives the N-alkylated azide (X), which is reduced by catalytic hydrogenation to the corresponding amine (XI). The hydrolysis of the ester group of (XI) with NaOH yields the free acetic acid derivative (XII), which is finally reductocondensed with ethyl 2-oxo-4-phenylbutyrate (XIII) by means of sodium cyanoborohydride.

Scheme 2:

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Scheme 3:

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Scheme 4:

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