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# SYNTHESIS OF A575C, A COMBINED ANGIOTENSIN CONVERTING ENZYME INHIBITOR - BETA ADRENOCEPTOR ANTAGONIST

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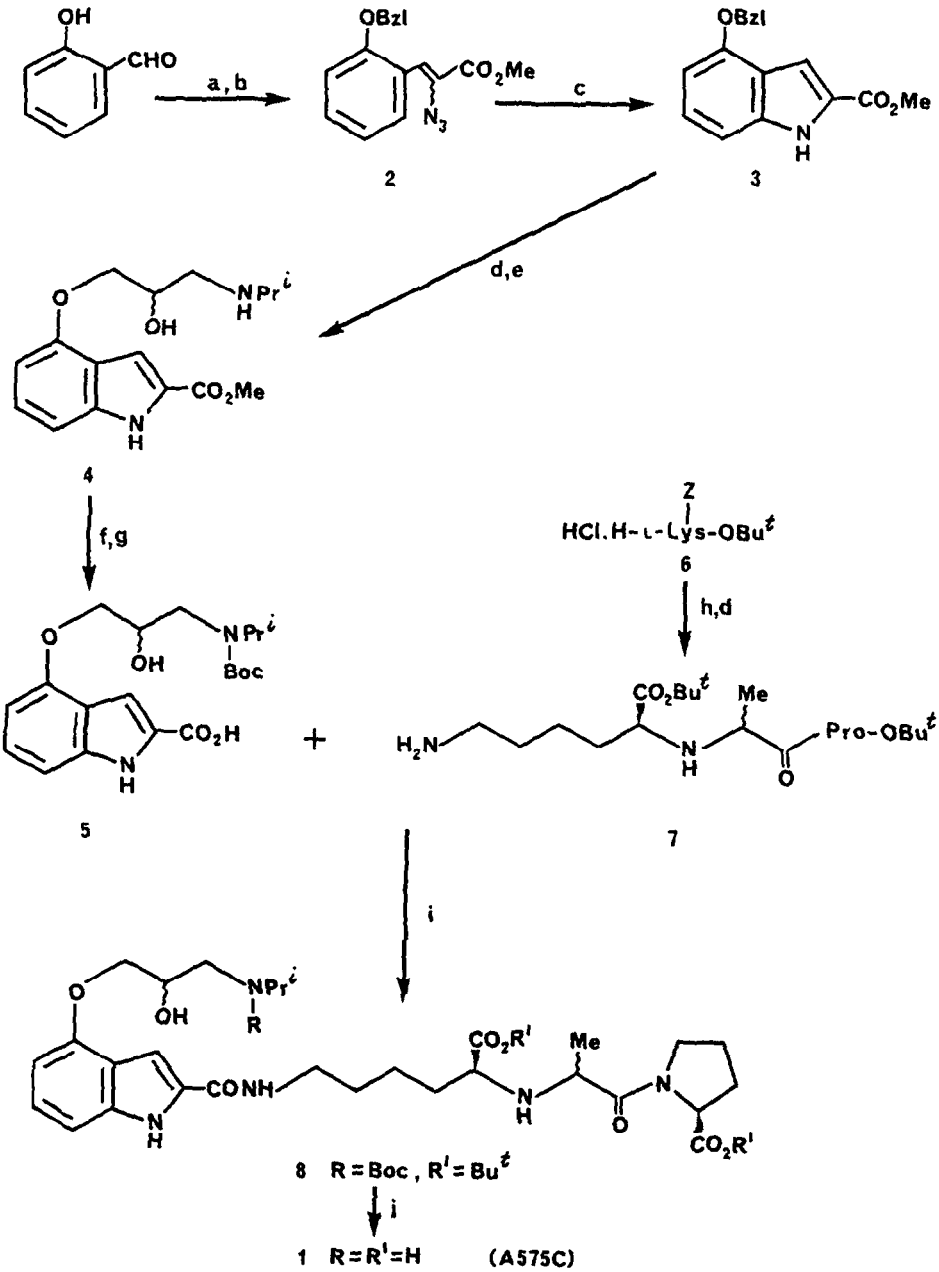
As part of a programme of research with the objective of developing a novel antihypertensive agent, we have prepared a compound which has both Angiotensin Converting Enzyme (ACE) inhibitor and beta-blocking activities. Agents with these individual activities have become well established, independently, as effective and well tolerated anti-hypertensives in several forms of human hypertension.[1,2] A compound which expresses both of these activities may have an improved therapeutic profile over an ACE inhibitor or beta-adrenoceptor antagonist alone. There have been a number of attempts in recent years to synthesise combination molecules designed to exhibit two distinct pharmacological activities, but successful examples of this approach are rare and more often these endeavours have ended in failure.[3] The failures undoubtedly reflect the intrinsic difficulty of accomodating the individual strucure-activity requirements in one molecule. This paper describes the synthesis of A575C, a compound which provides another successful example in which the combination approach has been applied to produce a molecule with dual activity.

N-1-(*S*)-Carboxy-5-[4-(3-isopropylamino-2(*R,S*)-hydroxypropoxy)-indole-2-carboxamido]pentyl-(*R,S*)-alanyl-(*S*)-proline **1**, (A575C) is a novel molecule which combines the essential features of a beta-blocker (pindolol[4]) and an ACE inhibitor (N-carboxyalkyldipeptide-type[5]) and expresses these activities both *in vivo* and *in vitro*.[6] A convergent synthesis of A575C is shown in the Scheme. The required 4-hydroxyindole derivative **3** was initially prepared from 2-benzyloxy-6-nitro-toluene *via* oxalate ester condensation and reductive (Fe/HOAc) cyclisation[7], however, the yield from the latter reaction was variable and the preparation of the starting material laborious. Consequently, we adopted the simpler methodology of Hemetsberger *et al*[8], which relies on the thermal cyclisation of the easily accessible intermediate azido-cinnamate **2** and reliably provides **3**, albeit in moderate overall yield (33%). Hydrogenolysis of **3** liberated the phenolic hydroxyl group which was elaborated to the beta-blocker oxypropanolamine side-chain




Reagents: a) BzlBr, $K_2CO_3$, $Me_2CO$, Δ ; b) $N_3CH_2CO_2Et$, NaOMe, MeOH; c) xylene, Δ ; d) $H_2$, Pd-C, MeOH; e) i: epibromohydrin, $KOBu^t$, DMF; ii: $Pr^iNH_2$, DMF, $H_2O$, Δ ; f) $Boc_2O$, DMF; g) NaOHaq, MeOH, Δ ; h) BrCH(Me)CO-L-Pro.$OBu^t$, $NaHCO_3$, MeCN, Δ ; i) DCCI, HOBt, $NEt_3$, DMF; j) $CF_3CO_2H$, anisole, $H_2O$ (9:1:1).

Scheme

by successive alkylation with epibromohydrin and ring opening with isopropylamine to give **4**. A variety of basic conditions were examined for the alkylation reaction (*eg* NaOH-$H_2O$-dioxan, NaH-DMF, $K_2CO_3$-DMF) but potassium *t*-butoxide in DMF gave the highest yield. The side-chain secondary amino-group was protected by reaction with di-*t*-butyl dicarbonate and the ester saponified to give the key synthon **5**.[9]

The required protected ACE-inhibitor fragment **7** was prepared by N-alkylation of the lysine derivative **6**[10] with *t*-butyl 2(*R,S*)-bromo-propionyl-(*S*)-prolinate [from bromopropionyl bromide and *t*-butyl prolinate[11]], followed by hydrogenolytic deprotection of the epsilon amino-group.

The coupling of **5** with **7** was mediated by DCCI-HOBt[12] and the product **8** isolated by silica gel chromatography {EtOAc - petrol(60-80) 1:1 *v/v*}, [71%, FAB-MS $(MH)^+$= 802]. Chromatographic analysis of the protected intermediate **8** showed the presence of two pairs of diastereoisomers approximately in the ratio 4:1.[13] Acidolytic deprotection of this mixture using TFA, with redistilled anisole as scavenger, and trituration with ether gave **1** as the analytically pure bistrifluoro-acetate salt, [94%, FAB-MS $(MH)^+$= 590].

In *in vitro* assays A575C was found to exhibit both ACE-inhibition [$IC_{50}$= 10.4 nM] and beta-adrenoceptor blockade [$pK_B$= 7.2] and hence the compound is potentially a novel type of antihypertensive agent. A detailed study of the biological activity of A575C has been published elsewhere.[6]

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13. The major pair of diastereoisomers could be separated from the minor pair, with difficulty, by column chromatography [$SiO_2$ (Merck 7734), EtOAc]. Preliminary data indicate that when deprotected as for **1** this preponderant pair has much reduced ACE inhibitory activity [$IC_{50}$ *ca* 320 nM]. This suggests that the configuration of the alanyl residue is *R* in this pair and that the more active *S*-isomer is present as the minor component. It has not proven possible either to obtain the minor pair of isomers in pure form or to separate the individual isomers. Stereospecific synthesis of individual diastereoisomers of A575C is in progress; subsequent publications will deal with the relationship between stereochemistry and activity in detail.

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