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A NEW SYNTHESIS OF 3-FLUORO PHENYLALANINE ESTERS

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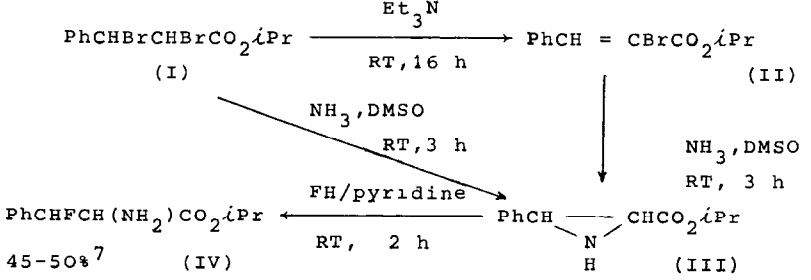
Summary : *Isopropyl 2-Phenyl 3-aziridinecarboxylate (III) obtained from isopropyl 2,3-dibromo-2,3-dihydrocinnamate (I) or isopropyl 2-bromocinnamate (II) reacts in mild conditions with hydrogen fluoride to give the isopropyl ester of 3-fluorophenylalanine (IV) in good yield.*

It is generally known and accepted now that the introduction of fluorine exerts an important and in many instances, useful influence on the bioactivity of organic molecules, and that many drugs act as enzyme inhibitors. Thus 3-fluoroalanine has similar antibactérial activity to that of chloramphenicol and tetracycline[1]. In view of this interest in fluorinated biologically active organic molecules, many synthetic and biological studies of aliphatic fluoro aminoacids have been developed [1-5].

However, concerning 2-amino-3-fluoro-3-arylalkanoic acid and ester derivatives, we have noted the failure of an early attempt to obtain 3-fluorophenylalanine ester [4] and only one procedure for the synthesis of 3-fluorophenylalanine from phenylserine and sulfur tetrafluoride [5]. Note that the latter is a gaseous reagent as toxic as phosgen. In a previous work, we have found that hydrogen fluoride reacts with aziridines to give 2-fluoro amines in good yields[6], and we here describe a convenient method of synthesis of ester derivatives of 3-fluoro phenylalanine (IV) from 2,3-dibromo-2,3-dihydro cinnamate (I) by the route given in the schema.



Isopropyl 2,3-dibromo-2,3-dihydrocinnamatewas obtained by bromination of isopropyl cinnamate,which was yielded by the action of isopropanol on the acid chloride of cinnamic acid.To a solution of this dibromo compound(I)(26mmol) in dry benzene,30mmol of triethylamine was added and stirring was maintained for 16h at room temperature;2-bromocinnamate(II) was thus obtained in quantitative yield.To a solution of the above dibromo compound(I),or the monobromo one (II)in dimethylsulfoxide,gaseous ammonia[8,9] was introduced for 3 hours.The solution was poured into a saturated solution of sodium chloride,extracted with benzene,washed with water,dried on magnesium sulfate,and then added to a 70% solution of FH in pyridine [10] contained in a polyethylene flask.After two hours' reaction at room temperature,the fluorinated compound (IV) was obtained in 45-50% [7] yield (from the dibromodihydrocinnamate(I)).m.p. of the hydrochlorid:182-183°C.(éthanol-éther).The ^{1}H NMR[11] spectrum of (IV){δTMS($CDCl_3$)} shows three signals at 1,17p.p.m.(6H,CH_3 of the isopropyl)a singulet at 1,63 p.p.m.(2H,NH_2,protons),two doublets centered at 3,51 and 3,93p.p.m.(C<u>H</u>(NH_2)), a septuplet at 5p.p.m.(1H,C<u>H</u>(CH_3)$_2$,two doublets centered at 5,32 and 6,1p.p.m. (1H,CHF),and a singulet at 7,34p.p.m.(5H,phenyl protons).The two methyl groups of the isopropyl are not equivalent,and so we have two overlaping doublets looking like a triplet.

^{19}F NMR[11]:The fluorine shift ØCCl$_3$F($CDCl_3$)is at 200p.p.m.,$^{2}J_{FH}$=47,6Hz, $^{3}J_{FH}$=26,6Hz.

The I.R. spectrum[11] shows ν_{NH_2} at 3350cm^{-1} and 3300cm^{-1}(sharp)and $\nu_{C=O}$= 1720cm^{-1}.

The indicated yield is that of the isolated compound.

We are presently attempting to develop this method to the synthesis of the other aliphatic amino acids.

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11. ^{19}FNMR with a Jeol, C - 60-H L (56MHz); ^{1}HNMR on a Varian A60; I.R. on a Leitz III G.

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