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DETERMINATION OF THREO AND ERYTHRO CONFIGURATIONS OF 3-FLUOROPHENYLALANINE FOR VERIFYING STEREOCHEMICAL ASPECTS OF RECENTLY REPORTED SYNTHESES

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Summary: Determination of threo and erythro configurations of both diastereoisomers of 3-fluorophenylalanine on the basis of chemical transformation and X-ray analysis has confirmed that the aziridine ring opening reaction gives the threo isomer stereoselectively, whereas the fluorodehydroxylation reaction affords both isomers nonselectively.

Increasing interest in the bioactivity of fluoroamino acids,[1] e.g., as irreversible enzyme inhibitors,[2] prompted the recent synthetic studies of 3-fluorophenylalanine using fluorodehydroxylation by Kollonitsch et al.[3] and aziridine ring opening reaction by Wade et al.[4] However, in these syntheses, the threo and erythro configurations of the products remained to be elucidated. In view of many specific activity examples shown by the hydroxyl substituent group in, e.g., chloramphenicol, ephedrin, and threonine, determination of the fluorine configuration is important for an understanding of the effects of fluorine substitution on biological activities of these related compounds. Thus, aiming at establishing stereoselective synthesis of both diastereoisomers of 3-fluorophenylalanine we have firstly examined stereochemistry of these known methods. We predicted nonselective formation of diastereoisomers for the former reaction as suggested by the proposed S_N1 type mechanism and a highly selective formation of one isomer for the latter as suggested by the ^{19}F NMR spectrum reported. Herein, we report the unequivocal determination of both threo and erythro configurations of 3-fluorophenylalanine on the basis of chemical and X-ray ananlysis evidence.

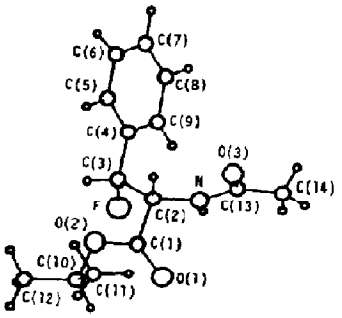
A modified fluorodehydroxylation of threo-β-phenylserine using diethylaminosulphur trifluoride instead of SF_4 in HF at -40°C for 2 hr, followed by chromatographic separation [Whatman cellulose powder CC31/1-PrOH (3 parts), H_2O (1 part), and NH_4OH (for 0.5 N concentration of the final solution) as eluent] yielded two isomeric fluoroamino acids [30% of each and 40% recovery of the starting material as determined by amino acid analysis]. ^1H and ^{19}F NMR spectra showed different characteristic signals for each isomer, A and B;[5] for A: ^1H NMR in D_2O (int. DSS) δ 4.14 (1H, dd, $J(H_\alpha F)$ 27, $J(H_\alpha H_\beta)$ 4.3 Hz, H_α), 6.14 (1H, dd, $J(H_\beta F)$ 45 Hz, H_β), 7.5 (5H, m, arom. H); ^{19}F NMR in D_2O (ext. C_6F_6) δ -25.3 (J 45, 27 Hz); for B: ^1H NMR δ 4.33 (1H, dd, $J(H_\alpha F)$ 16, $J(H_\alpha H_\beta)$ 3.4 Hz, H_α), 6.17 (1H, dd, $J(H_\beta F)$ 44 Hz, H_β),~7.4 (5H, m, arom. H); ^{19}F NMR δ -21.3 (J 44, 16 Hz). These facts obviously showed that the fluorodehydroxylation reaction was nonselective.

Meanwhile, the aziridine ring opening reaction was followed and confirmed to give the product 3-fluorophenylalanine 2-propyl ester, which showed only one kind of ^{19}F NMR spectrum as described in literature.[4] The attempted ester cleavage of this product failed due to

facile defluorination. For structural elucidation, a mixture of the previously obtained amino acid isomers, A (2 parts) and B (1 part) was esterified to produce the corresponding mixture of 3-fluorophenylalanine 2-propyl esters as HCl salts. The major component of the mixture, which was derived from isomer A, was identical to the compound obtained from the aziridine ring opening reaction by comparison of ^{19}F and ^{1}H NMR spectra. Thus, the reaction was demonstrated to be highly stereoselective in contrast to the fluorodehydroxylation one.

For elucidating the threo or erythro configuration, the 2-PrOH ester of isomer A was acetylated and recrystallized [hexane-ether] to afford fine crystals for X-ray analysis;[6] m.p. 79-80°C.

The configuration was the threo one depicted below.



Finally, it should be pointed out that a similar ring opening reaction has been reported to give threonine but not allo-threonine regardless of the cis or trans configuration of the starting aziridine carboxylates,[7] although the reaction mechanism remains to be established. Thus, both aziridine ring opening reactions appear to proceed by the same mechanism.

Our next paper reports a stereoselective synthesis of erythro-3-fluorophenylalanine which we developed.

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5. Chromatographic separation of both isomers was not successful but fractional recrystallization yielded isomer A with an approximate purity of 90%. Experimental details will be reported in the full paper.
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