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ORGANIC FLUORINE COMPOUNDS—XXXVIII[1]

N-ALKYLATED FLUOROAMINO ACIDS

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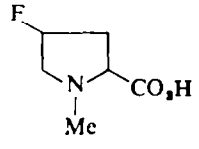
Abstract—Hydroxyproline methyl ester was methylated and the hydroxyl group of the product replaced by fluorine, using 1,1,2-trifluoro-2-chloroethyl-diethylamine. Analogously, the N,N-dimethyl derivatives of several β-hydroxy-α-amino acids were transformed into the corresponding β-fluoro compounds.

VERY few fluorinated aliphatic amino acids have been synthesized although they may be antimetabolites to the natural amino acids. 5-Fluoronorvaline and 6-fluoronorleucine,[2] γ-fluoroglutamic acid,[3,4] fluoro- and difluoro-α-aminoisobutyric acid[5] and α-fluoro-β-alanine[6] are the only known representatives of this class. The possibility of transforming β- or γ-hydroxy-α-amino acids into β- or γ-fluoro-α-amino acids by reaction with 1,1,2-trifluoro-2-chloroethyl-diethylamine[8] was studied but failed when the amino group was free. However, in a series of N,N-disubstituted amino acids, the reaction proceeded smoothly. The methyl esters of the hydroxyamino acids were fully methylated on the nitrogen atom and the hydroxyl replaced by fluorine with the above-mentioned reagent. The methylation was carried out by Bowman's method (reaction with formaldehyde and subsequent catalytic hydrogenation.)[9] Thus the following compounds have been obtained: N-methyl-4-fluoroproline (I), N,N-dimethyl-α-amino-β-fluorobutyric acid (II, R = Me), N,N-dimethyl-β-fluoro-α-alanine (II, R = H), N,N-dimethyl-β-fluoro-phenylalanine (II, R = Ph) and N,N-dimethyl-β-fluoro-O-carbethoxytyrosine (II, R = EtOCO·C_6H_4), the last two in form of their ethyl esters.



I

R·CHF·CH(NMe₂)·COOH

II

[1] Part XXXVII: I. Shahak and E. D. Bergmann, *J. Chem. Soc.* 1966, in press.
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[3] M. Hudlicky, *Tetrahedron Letters* No. 14, 21 (1960).
[4] R. L. Buchanan, F. H. Dean and F. C. M. Pattison, *Canad. J. Chem.* **40**, 1571 (1962).
[5] E. D. Bergmann and A. Shani, *J. Chem. Soc.* 3462 (1963).
[6] E. D. Bergmann and S. Cohen, *J. Chem. Soc.* 4669 (1961).
[7] For some unsaturated fluorinated α-amino acids, see V. Tolman and K. Veres, *Tetrahedron Letters* 1967 (1964). E. D. Bergmann and A. Cohen, *Tetrahedron Letters* 2085 (1965).
[8] Cf. also for literature, E. D. Bergmann and A. Cohen, *Israel J. Chem.* **3**, 71 (1965).
[9] R. E. Bowman, *J. Chem. Soc.* 1346 (1950). Cf. T. Suyama and S. Kanao, *Yakugaku Zasshi* **85**, 284 (1965) (*Chem. Abstr.* **63**, 7095 (1965)).

EXPERIMENTAL

N-Methylhydroxyproline methyl ester. A mixture of 13·1 g L-hydroxypyroline and 150 ml HCl-saturated MeOH was kept at room temp for 48 hr, the solvent evaporated *in vacuo* and the residue washed with anhydrous ether and dissolved in 200 ml anhydrous MeOH. To this soln was added 4 g Pd–C (10%), 20 g paraformaldehyde and 10 g $MgSO_4$, and the mixture hydrogenated at 4 atm press. The filtered soln was evaporated *in vacuo* and the residue taken up in a small quantity of water and treated with an excess of K_2CO_3 (with cooling). Extraction with CH_2Cl_2 gave the desired ester, b.p. 102°/0·5 mm; yield, 13 g (81%). (Found: C, 52·6; H, 8·3. $C_7H_{13}NO_3$ requires C, 52·8; H, 8·2%.)

N-Methyl-4-fluoroproline methyl ester. A mixture of 5 g of the foregoing compd, 200 ml CH_2Cl_2 and 11·8 g 1,1,2-trifluoro-2-chloroethyl-diethylamine[10] was prepared at 0° and kept at this temp for 36 hr in a well-stoppered bottle and extracted 3 times with 10 ml cold water. The aq soln was saturated at 0° with K_2CO_3 and extracted thoroughly with CH_2Cl_2. Distillation *in an efficient column* gave the desired ester, b.p. 73–75°/3 mm; yield, 1·5 g (33%). (Found: C, 52·1; H, 7·7; N, 8·7; F, 11·5. $C_7H_{12}FNO_2$ requires: C, 52·2; H, 7·5; N, 8·7; F, 11·8%.)

N-Methyl-4-fluoroproline (I) *hydrochloride.* When the ester (1 g) was refluxed for 2·5 hr with 10% HCl and the soln evaporated *in vacuo*, an 80% yield (850 mg) of the hydrochloride of the free acid was obtained; after trituration with acetone and recrystallization from iso-PrOH–ether, hygroscopic crystals of m.p. 190°. (Found: C, 39·4; H, 5·9; F, 10·0. $C_6H_{11}ClFNO_2$ requires C, 39·2; H, 6·0; F, 10·3%.)

N,N-Dimethyl-DL-serine methyl ester was prepared in the same manner as the proline derivative; yield, 70%, b.p. 108–109°/25 mm. *Hydrochloride*, m.p. 127°, from iso-PrOH. (Found: C, 38·9; H, 7·7. $C_6H_{14}ClNO_3$ requires: C, 39·2; H, 7·6%.)

N,N-Dimethyl-β-fluoro-α-alanine methyl ester hydrochloride. From 10 g of the foregoing ester, 2·5 g of the desired fluoro- compd was obtained, the remainder decomposing during the heating; b.p. 80–90°/25 mm. This fraction was purified by transformation into its hydrochloride (in ether with gaseous HCl). From iso-PrOH, 1 g (10%) of m.p. 161°. (Found: C, 38·5; H, 6·8; F, 9·9; N, 7·5. $C_6H_{13}ClFNO_2$ requires: C, 38·9; H, 7·0; F, 10·2; N, 7·6%.)

N,N-Dimethyl-β-fluoro-α-alanine (II, R = H) *hydrochloride.* The ester hydrochloride (400 mg) was refluxed for 3 hr with 10% HCl and the soln evaporated to dryness *in vacuo*. The residue was triturated with acetone and recrystallized from iso-PrOH, m.p. 203–204°; yield, 0·26 g (60%). (Found: C, 34·8; H, 6·7; F, 10·7. $C_5H_{11}ClFNO_2$ requires C, 35·0; H, 6·4; F, 11·1%.)

N,N-Dimethyl-DL-threonine methyl ester was prepared analogously; yield, 90%; b.p. 98°/25 mm. (Found: C, 52·2; H, 9·5. $C_7H_{15}NO_3$ requires: C, 52·2; H, 9·3%.)

Methyl N,N-dimethyl-α-amino-β-fluorobutyrate. From 5 g of the foregoing ester, 3 g (60%) fluorinated ester was obtained; b.p. 82–85°/25 mm. (Found: C, 51·5; H, 8·7; F, 11·3. $C_7H_{14}FNO_2$ requires: C, 51·5, H, 8·6; F, 11·6%.)

N,N-Dimethyl-α-amino-β-fluorobutyric acid (II, R = Me) *hydrochloride.* Boiling 10% HCl caused hydrolysis of the foregoing ester. The product (yield, 60%) melted at 157° after trituration with acetone and recrystallization from iso-PrOH–ether. (Found: C, 38·6; H, 6·7; F, 9·9. $C_6H_{13}ClFNO_2$ requires C, 38·9; H, 7·0; F, 10·2%.)

N,N-Dimethyl-β-phenylserine ethyl ester hydrochloride was prepared from ethyl phenylserinate[11] hydrochloride and paraformaldehyde as described. After the reduction was completed, the mixture was heated to b.p. and filtered. The product crystallized upon cooling and was recrystallized from EtOH; yield, 60%; m.p. 196°. (Found: C, 57·1; H, 7·3. $C_{13}H_{20}ClNO_3$ requires C, 57·1; H, 7·3%.)

N,N-Dimethyl-β-fluorophenylalanine (II, R = PH) *ethyl ester.* The foregoing hydrochloride (13·8 g) in a small quantity water was treated with K_2CO_3 and the free ester transferred into 300 ml CH_2Cl_2. To the well-dried soln, 18·9 g of 1,1,2-trifluoro-2-chloroethyl-diethylamine was added at 0°, and the mixture kept at 0° for 24 hr and then at room temp for 8 hr and poured into cold K_2CO_3 aq. The organic layer was distilled *in vacuo*: (a) N,N-diethyl-chlorofluoroacetamide, b.p. 70°/0·5 mm; (b) N,N-dimethyl-β-fluorophenylalanine methyl ester, b.p. 115–120°/0·8 mm; yield, 9·5 g (80%). (Found: F, 8·4. $C_{13}H_{18}FNO_2$ requires: 8·0%.)

[10] E. D. Ayer, *J. Med. Chem.* **6**, 608 (1963).

[11] E. D. Bergmann, H. Bendas and W. Taub, *J. Chem. Soc.* 2673 (1951).

Hydrochloride, prepared with gaseous HCl in dry ether, from iso-PrOH, m.p. 182°. (Found: C, 56·9; H, 7·1; F, 7·3. $C_{12}H_{15}ClFNO_2$ requires C, 56·7; H, 7·0; F, 7·0%.)

We did not succeed in hydrolysing the ester to the free acid without at least partial loss of the fluorine.

N,N-*Dimethyl-β-fluorophenylalanine amide* was obtained from the preceding hydrochloride by treatment with a saturated EtOH soln of ammonia. From cyclohexane, m.p. 118–120°; yield, 30%. (Found, N, 12·8; F, 8·6. $C_{11}H_{15}FN_2O$ requires N, 13·2; F, 9·0%.)

Hydrochloride, from iso-PrOH–ether, m.p. 199–200°. (Found: F, 8·1; N, 11·1. $C_{11}H_{16}ClFN_2O$ requires: F, 7·7; N, 11·4%.)

N,N-*Dimethyl*-p-(O-*carbethoxy*)-*β-phenylserine ethyl ester hydrochloride* was prepared in 70% yield from *p*-(O-carbethoxy)-*β*-phenylserine ethyl hydrochloride,[12] as described above. From EtOH, m.p. 215°. (Found: C, 53·3; H, 6·6; N, 3·8. $C_{16}H_{24}ClNO_6$ requires C, 53·1; H, 6·7; N, 3·9%.)

N,N-*Dimethyl*-p-(O-*carbethoxy*)-*β-fluoro-phenylalanine* (II, R = $C_2H_5OCO{\cdot}C_6H_4$) *ethyl ester hydrochloride*. As described for the unsubstituted phenylalanine deriv, the free ester was prepared from the preceding hydrochloride and treated in 100 ml CH_2Cl_2 with 3·8 g 1,1,2-trifluoro-2-chloro-ethyl-diethylamine at 0° for 24 hr and then at room temp for 8 hr. The fluorinated ester so obtained was converted into its hydrochloride by treatment of its etheral soln with gaseous HCl, yield, 3·2 g (90%); from iso-PrOH–ether, m.p. 158–159°. (Found: C, 52·7; H, 6·6; F, 4·9. $C_{16}H_{23}ClFNO_5$ requires C, 52·9; H, 6·3; F, 5·2%.

[12] K. W. Rosenmund and H. Dornsaft, *Dtsch. Chem. Ber. Ges.* **52**, 1734 (1919).